AN AMERICAN TEXT-BOOK

OF

PHYSIOLOGY

BY

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PREFACE.

THE collaboration of several teachers in the preparation of an elementary text-book of physiology is unusual, the almost invariable rule heretofore having been for a single author to write the entire book. It does not seem desirable to attempt a discussion of the relative merits and demerits of the two plans, since the method of collaboration is untried in the teaching of physiology, and there is therefore no basis for a satisfactory comparison. It is a fact, however, that many teachers of physiology in this country have not been altogether satisfied with the text-books at their disposal. Some of the more successful older books have not kept pace with the rapid changes in modern physiology, while few, if any, of the newer books have been uniformly satisfactory in their treatment of all parts of this many-sided science. Indeed, the literature of experimental physiology is so great that it would seem to be almost impossible for any one teacher to keep thoroughly informed on all topics. This fact undoubtedly accounts for some of the defects of our present text-books, and it is hoped that one of the advantages derived from the collaboration method is that, owing to the less voluminous literature to be consulted, each author has been enabled to base his elementary account upon a comprehensive knowledge of the part of the subject assigned to him. Those who are acquainted with the difficulty of making a satisfactory elementary presentation of the complex and oftentimes unsettled questions of physiology must agree that authoritative statements and generalizations, such as are frequently necessary in text-books if they are to leave any impression at all upon the student, are usually trustworthy in proportion to the fulness of information possessed by the writer.

Perhaps the most important advantage which may be expected to follow the use of the collaboration method is that the student gains thereby the point of view of a number of teachers. In a measure he reaps the same benefit as would be obtained by following courses of instruction under different teachers. The different standpoints assumed, and the differences in emphasis laid upon the various lines of procedure, chemical, physical, and anatomical, should give the student a better insight into the methods of the science as it exists

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to-day. A similar advantage may be expected to follow the inevitable over-lapping of the topics assigned to the various contributors, since this has led in many cases to a treatment of the same subject by several writers, who have approached the matter under discussion from slightly varying standpoints, and in a few instances have arrived at slightly different conclusions. In this last respect the book reflects more faithfully perhaps than if written by a single author the legitimate differences of opinion which are held by physiologists at present with regard to certain questions, and in so far it fulfils more perfectly its object of presenting in an unprejudiced way the existing state of our knowledge. It is hoped, therefore, that the diversity in method of treatment, which at first sight might seem to be disadvantageous, will prove to be the most attractive feature of the book.

In the preparation of the book it has been assumed that the student has previously obtained some knowledge of gross and microscopic anatomy, or is taking courses in these subjects concurrently with his physiology. For this reason no systematic attempt has been made to present details of histology or anatomy, but each author has been left free to avail himself of material of this kind according as he felt the necessity for it in developing the physiological side.

In response to a general desire on the part of the contributors, references to literature have been given in the book. Some of the authors have used these freely, even to the point of giving a fairly complete bibliography of the subject, while others have preferred to employ them only occasionally, where the facts cited are recent or are noteworthy because of their importance or historical interest. References of this character are not usually found in elementary text-books, so that a brief word of explanation seems desirable. It has not been supposed that the student will necessarily look up the references or commit to memory the names of the authorities quoted, although it is possible, of course, that individual students may be led to refer occasionally to original sources, and thereby acquire a truer knowledge of the subject. The main result hoped for, however, is a healthful pedagogical influence. It is too often the case that the student of medicine, or indeed the graduate in medicine, regards his text-book as a final authority, losing sight of the fact that such books are mainly compilations from the works of various investigators, and that in all matters in dispute in physiology the final decision must be made, so far as possible, upon the evidence furnished by experimental work. To enforce this latter idea and to indicate the character and source of the great literature from which the material of the text-book is obtained have been the main reasons for the adoption of the reference system. It is hoped also that the

book will be found useful to many practitioners of medicine who may wish to keep themselves in touch with the development of modern physiology. For this class of readers references to literature are not only valuable, but frequently essential, since the limits of a text-book forbid an exhaustive discussion of many points of interest concerning which fuller information may be desired.

The numerous additions which are constantly being made to the literature of physiology and the closely related sciences make it a matter of difficulty to escape errors of statement in any elementary treatment of the subject. It cannot be hoped that this book will be found entirely free from defects of this character, but an earnest effort has been made to render it a reliable repository of the important facts and principles of physiology, and, moreover, to embody in it, so far as possible, the recent discoveries and tendencies which have so characterized the history of this science within the last few years.

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AN AMERICAN
TEXT-BOOK OF PHYSIOLOGY.

I. INTRODUCTION.

THE term "physiology" is, in an etymological sense, synonymous with "natural philosophy," and occasionally the word is used with this significance even at the present day.[1] By common usage, however, the term is restricted to the living side of nature, and is meant to include the sum of our knowledge concerning the properties of living matter. The active substance of which living things are composed is supposed to be closely similar in all cases, and is commonly designated as protoplasm (πρῶτος, first, and πλάσμα, anything formed). It is usually stated that this word was first introduced into biological literature by the botanist Von Mohl to designate the granular semi-liquid contents of the plant-cell. It seems, however, that priority in the use of the word belongs to the physiologist Purkinje (1840), who employed it to describe the material from which the young animal embryo is constructed.[2] In recent years the term has been applied indifferently to the soft material constituting the substance of either animal or plant-cells. The word must not be misunderstood to mean a substance of a definite chemical nature or of an invariable morphological structure; it is applied to any part of a cell which shows the properties of life, and is therefore only a convenient abbreviation for the phrase "mass of living matter."

Living things fall into two great groups, animals and plants, and corresponding to this there is a natural separation of physiology into two sciences, one dealing with the phenomena of animal life, the other with plant life. In what follows in this introductory section the former of these two divisions is chiefly considered, for although the most fundamental laws of physiology are, without doubt, equally applicable to animal and vegetable protoplasm, nevertheless the structure as well as the properties of the two forms of matter are in some respects noticeably different, particularly in the higher types of organisms in each group. The most striking contrast, perhaps, is found in the fact that plants exhibit a lesser degree of specialization in form and function and

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[1] See *Mineral Physiology and Physiography*, T. Sterry Hunt, 1886.
[2] O. Hertwig: *Die Zelle und die Gewebe*, 1893.

a much greater power of assimilation. Owing to this latter property the plant-cell is able, with the aid of solar energy, to construct its protoplasm from very simple forms of inorganic matter, such as water, carbon dioxide, and inorganic salts. In this way energy is stored within the vegetable cell in the form of complex organic compounds. Animal protoplasm, on the contrary, has comparatively feeble synthetic properties; it is characterized chiefly by its destructive power. In the long run, animals obtain their food from the plant kingdom, and the animal cell is able to dissociate or oxidize the complex material of vegetable protoplasm and thus liberate the potential energy contained therein, the energy taking the form mainly of heat and muscular work. We must suppose that there is a general resemblance in the ultimate structure of animal and vegetable living matter to which the fundamental similarity in properties is due, but at the same time there must be also some common difference in internal structure between the two, and it is fair to assume that the divergent properties exhibited by the two great groups of living things are a direct outcome of this structural dissimilarity; to make use of a figure of speech employed by Bichat, plants and animals are cast in different moulds.

It is difficult if not impossible to settle upon any one property which absolutely shall distinguish living from dead matter. Nutrition, that is, the power of converting dead food material into living substance, and reproduction, that is, the power of each organism to perpetuate its kind by the formation of new individuals, are probably the most fundamental characteristics of living things; but in some of the specialized tissues of higher animals the power of reproduction, so far as this means mere multiplication by cell-division, seems to be lost, as, for example, in the case of the nerve-cells in the central nervous system or of the ovum itself before it is fertilized by the spermatozoon. Nevertheless these cellular units are indisputably living matter, and continue to exhibit the power of nutrition as well as other properties characteristic of the living state. It is possible also that the power of nutrition may, under certain conditions, be held in abeyance temporarily at least, although it is certain that a permanent loss of this property is incompatible with the retention of the living condition.

It is frequently said that the most general property of living matter is its irritability. The precise meaning of the term vital irritability is hard to define. The word implies the capability of reacting to a stimulus and usually also the assumption that in the reaction some of the inner potential energy of the living material is liberated, so that the energy of the response is many times greater, it may be, than the energy of the stimulus. This last idea is illustrated by the case of a contracting muscle, in which the stimulus acts as a liberating force causing chemical decompositions of the substance of the muscle with the liberation of a comparatively large amount of energy, chiefly in the form of heat or of heat and work. It may be remarked in passing, however, that we are not justified at present in assuming that a similar liberation of stored energy takes place in all irritable tissues. In the case of nerve-fibres, for instance, we have a typically irritable tissue which responds readily to

external stimuli, but as yet it has not been possible to show that the formation or conduction of a nerve impulse is accompanied by or dependent upon the liberation of potential chemical energy. The nature of the reaction of irritable living matter is found to vary with the character of the tissue or organism on the one hand, and, so far as intensity goes at least, with the nature of the stimulus on the other. Response of a definite character to appropriate external stimulation may be observed frequently enough in dead matter, and in some cases the nature of the reaction simulates closely some of those displayed by living things. For instance, a dead catgut string may be made to shorten after the manner of a muscular contraction by the appropriate application of heat, or a mass of gunpowder may be exploded by the action of a small spark and give rise to a great liberation of energy which had previously existed in potential form within its molecules. As regards any piece of matter we can only say that it exhibits vital irritability when the reaction or response it gives upon stimulation is one characteristic of living matter in general or of the particular kind of living matter under observation; thus, a muscle-fibre contracts, a nerve-fibre conducts, a gland-cell secretes, an entire organism moves or in some way adjusts itself more perfectly to its environment. Considered from this standpoint, irritability means only the exhibition of one or more of the peculiar properties of living matter and cannot be used to designate a property in itself distinctive of living structure; the term, in fact, comprises nothing more specific or characteristic than is implied in the more general phrase vitality. When an amœba dies it is no longer irritable, that is, its substance no longer assimilates when stimulated by the presence of appropriate food, its conductivity and contractility disappear so that mechanical irritation no longer causes the protrusion or retraction of pseudopodia—no form of stimulation, in fact, is capable of calling forth any of the recognized properties of living matter. To ascertain, therefore, whether or not a given piece of matter possesses vital irritability we must first become acquainted with the fundamental properties of living matter in order to recognize the response, if any, to the form of stimulation used.

Nutrition or assimilation, in a wide sense of the word, has already been referred to as probably the most universal and characteristic of these properties. By this term we designate that series of changes through which dead matter is received into the structure of living substance. The term in its broadest sense may be used to cover the subsidiary processes of digestion, respiration, absorption, and excretion through which food material and oxygen are prepared for the activity of the living molecules, and the waste products of activity are removed from the organism, as well as the actual conversion of dead material into living protoplasm. This last act, which is presumably a synthetic process effected under the influence of living matter, is especially designated as anabolism or as assimilation in a narrower sense of the word as opposed to disassimilation. By disassimilation or katabolism we mean those changes leading to the destruction of the complex substance of the living molecules, or of the food material in contact with these molecules.

As was said before, animal protoplasm is pre-eminently katabolic, and the evidence of its katabolism is found in the waste products, such as CO_2, H_2O, and urea, which are given off from animal organisms. Assimilation and disassimilation, or anabolism and katabolism, go hand in hand and together constitute an ever-recurring cycle of activity which persists as long as the material retains its living structure and which as a whole is designated under the name metabolism. In most forms of living matter metabolism is in some way self-limited, so that gradually it becomes less perfect, old age comes on, and finally death ensues. It has been asserted that originally the metabolic activity of protoplasm was self-perpetuating—that, barring accident, the cycle of changes would go on forever. Resting upon this assumption it has been suggested by Weissmann that the protoplasm of the reproductive elements still retains this primitive and perfect metabolism and thus provides for the continuity of life. The speculations bearing upon this point will be discussed in more detail in the section on Reproduction.

Reproduction in some form is also practically a universal property of living matter. The unit of structure among living organisms is the cell. Under proper conditions of nourishment the cell may undergo separation into two daughter cells. In some cases the separation takes place by a simple act of fission, in other cases the division is indirect and involves a number of interesting changes in the structure of the nucleus and the protoplasm of the body of the cell, or cytoplasm, as it is frequently called. In the latter case the process is spoken of as karyokinesis or mitosis. This act of division was supposed formerly to be under the control of the nucleus of the cell, but modern histology has shown that in karyokinetic division the process, in many cases at least, is initiated by a special structure to which the name centrosome has been given. The many-celled animals arise by successive divisions of a primitive cell, the ovum, and in the higher forms of life the ovum requires to be fertilized by union with a spermatozoon before cell-division becomes possible. The sperm-cell acts as a stimulus to the egg-cell (see section on Reproduction) and rapid cell-division is the result of their union. It must be noted also that the term reproduction includes the power of hereditary transmission. The daughter-cells are similar in form to the parent-cell and the organism produced from a fertilized ovum is substantially a facsimile of the parent forms. Living matter, therefore, not only exhibits the power of separating off other units of living matter, but of transmitting to its progeny its own peculiar internal structure and properties.

Contractility and conductivity are properties exhibited in one form or another in all animal organisms and we must believe that they are to be counted among the primitive properties of protoplasm. The power of contracting or shortening is, in fact, one of the commonly recognized features of a living thing. It is generally present in the simplest forms of animal as well as vegetable life, although in the more specialized forms it is found for the most part only in animal organisms. The opinion seems to be general among physiologists that wherever this property is exhibited, whether in the

formation of the pseudopodia of an amœba or white blood-corpuscle, or in the vibratile movements of ciliary structures, or in the powerful contractions of voluntary muscle, the underlying mechanism by which the shortening is produced is essentially the same throughout. However general the property may be, it cannot be considered as distinctively characteristic of living structure. As was mentioned before, Engelmann[1] has been able to show that a dead catgut string when surrounded by water of a certain temperature and exposed to a sudden additional rise of temperature will contract or shorten in a manner closely analogous to the contraction of ordinary muscular tissue, and it is not at all impossible that the molecular processes involved in the shortening of the catgut string and the muscle-fibre may be essentially the same.

That conductivity is also a fundamental property of primitive protoplasmic structure seems to be assured by the reactions which the simple motile forms of life exhibit when exposed to external stimulation. An irritation applied to one point of a protoplasmic mass may produce a reaction involving other parts, or indeed the whole extent of the organism. The phenomenon is most clearly exhibited in the more specialized animals which possess a distinct nervous system. In these forms a stimulus applied to one organ, as for instance light acting upon the eye, may be followed by a reaction involving quite distant organs, such as the muscles of the extremities; we know that in these cases the irritation has been conducted from one organ to the other by means of the nervous tissues. But here also we have a property which is widely exhibited in inanimate nature. The conduction of heat, electricity, and other forms of energy is familiar to every one. While it is quite possible that conduction through the substance of living protoplasm is something *sui generis*, and does not find a strict parallel in dead structures, yet it must be admitted that it is conceivable that the molecular processes involved in nerve conduction may be essentially the same as prevail in the conduction of heat through a solid body, or in the conduction of a wave of pressure through a liquid mass. At present we know nothing definite as to the exact nature of vital conduction, and can therefore affirm nothing.

The four great properties enumerated, namely, nutrition or assimilation (including digestion, secretion, absorption, excretion, anabolism, and katabolism), reproduction, conduction, and contractility, form the important features which we may recognize in all living things and which we make use of in distinguishing between dead and living matter. A fifth property perhaps should be added, that of sensibility or sensation, but concerning this property as a general accompaniment of living structure our knowledge is extremely imperfect; something more as to the difficulties connected with this subject will be said presently. The four fundamental properties mentioned are all exhibited in some degree in the simplest forms of life, such as the protozoa. In the more highly organized animals, however, we find that specialization of function prevails. Hand in hand with the differentiation in form which is displayed in the structure of the constituent tissues there goes a specialization

[1] *Ueber den Ursprung der Muskelkraft*, Leipzig, 1893.

in certain properties with a concomitant suppression of other properties, the outcome of which is that muscular tissue exhibits pre-eminently the power of contractility, the nerve tissues are characterized by a highly developed power of conductivity, and so on. While in the simple unicellular forms of animal life the fundamental properties are all somewhat equally exhibited within the compass of a single unit or cell, in the higher animals we have to deal with a vast community of cells segregated into tissues each of which possesses some distinctive property. This specialization of function is known technically as the physiological division of labor. The beginning of this process may be recognized in the cell itself. The typical cell is already an organism of some complexity as compared with a simple mass of undifferentiated protoplasm. The protoplasm of the nucleus, particularly of that material in the nucleus which is designated as chromatin, is differentiated, both histologically and physiologically, from the protoplasm of the rest of the cell, the so-called cytoplasm. The chromatin material in the resting cell is arranged usually in a network, but during the act of division (karyokinesis) it is segmented into a number of rods or filaments known as chromosomes. In the ovum there are good reasons for believing that the power of transmitting hereditary characteristics has been especially acquired by these chromosomes. The nucleus, moreover, controls in some way the metabolism of the entire cell, for it has been shown, in some cells at least, that a non-nucleated piece of the cytoplasm is not only deprived of the power of reproduction, but has also such limited powers of nutrition that it quickly undergoes disintegration. On the other hand contractility and conductivity, and some of the functions connected with nutrition, such as digestion and excretion, seem often to be specialized in the cytoplasm. As a further example of differentiation in the cell itself the existence of the centrosome may be referred to. The centrosome is a body of very minute size which has been discovered in numerous kinds of cells. It is considered by many observers to be a permanent structure of the cell, lying either in the cytoplasm, or possibly in some cases within the substance of the nucleus. When present it seems to have some special function in connection with the movements of the chromosomes during the act of cell-division. In the many-celled animals the primitive properties of protoplasm become highly developed, in consequence of this subdivision of function among the various tissues, and in many ways the most complex animals are, from a physiological standpoint, the simplest for purposes of study, since the properties of living matter become separated and emphasized in them to such an extent that they are better fitted for accurate observation.

We are at liberty to suppose that the various properties so clearly recognizable in the differentiated tissues of higher animals are all actually or potentially contained in the comparatively undifferentiated protoplasm of the simplest unicellular forms. That the lines of variation, or in other words the direction of specialization in form and function, are not infinite, but on the contrary comparatively limited, seems evident when we reflect that in spite of the numerous branches of the phylogenetic stem the properties as well as the

forms of the differentiated tissues throughout the animal kingdom are strikingly alike. Striated muscle, with the characteristic property of sharp and powerful contraction, is everywhere found; the central nervous system in the invertebrates is built upon the same type as in the highest mammals, and the variations met with in different animals are probably but varying degrees of perfection in the development of the innate possibility contained in primitive protoplasm. It is not too much to say, perhaps, that were we acquainted with the structure and chemistry of the ultimate units of living substance, the key to the possibilities of the evolution of form and function would be in our possession.

Most interesting suggestions have been made in recent years as to the essential molecular structure of living matter. These views are necessarily very incomplete and of a highly speculative character, and their correctness or incorrectness is at present beyond the range of experimental proof; nevertheless they are sufficiently interesting to warrant a brief statement of some of them, as they seem to show at least the trend of physiological thought.

Pflüger,[1] in a highly interesting paper upon the nature of the vital processes, calls attention to the great instability of living matter. He supposes that living substance consists of very complex and very unstable molecules of a proteid nature which, because of the active intra-molecular movement present, are continually dissociating or falling to pieces with the formation of simpler and more stable bodies such as water, carbon dioxide and urea, the act of dissociation giving rise to a liberation of energy. "The intra-molecular heat (movement) of the cell is its life." He suggests that in this living molecule the nitrogen is contained in the form of a cyanogen compound, and that the instability of the molecule depends chiefly upon this particular grouping. Moreover the power of the molecule to assimilate dead proteid and convert it to living proteid like itself he attributes to the existence of the cyanogen group. It is known that cyanogen compounds possess the property of polymerization, that is, of combining with similar molecules to form more complex molecules, and we may suppose that the molecules of dead proteid when brought into contact with the living molecules are combined with the latter by a process analogous to polymerization or condensation. By this means the stable structure of dead proteid is converted to the labile structure of living proteid, and the molecules of the latter increase in size and instability. When living substance dies its molecules undergo alteration and become incapable of exhibiting the usual properties of life. Pflüger suggests that the change may consist essentially in an absorption of water whereby the cyanogen grouping passes over into an ammonia grouping. Loew[2] assumes also that the difference between dead and living or active proteid lies chiefly in the fact that in the latter we have a very unstable or labile molecule in which the atoms are in active motion. The instability of the molecules he likewise attributes to

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[1] *Archiv für die gesammte Physiologie*, 1875, Bd. 10, p. 251.

[2] *Ibid.*, 1880, Bd. 22; Loew and Bokorny: *Die chemische Kraftquelle in lebenden Protoplasma*, München, 1882; Imperial Institute of Tokyo (College of Agriculture), 1894.

the existence of certain groupings of the atoms. Influenced in part by the power of living material to reduce alkaline silver solutions, he supposes that the specially important labile group in the molecule is the aldehyde radical $-C{=O \atop -H}$. The nitrogen exists also in a labile amido- combination, $-NH_2$, and the active or living form of these two groups may be expressed by the formula ${-CH-NH_2 \atop =C \quad -C{=O \atop -H}}$. If this grouping by chemical change became converted to the grouping ${-CH-NH \atop =C \quad -CHOH}$, it would form a comparatively inert compound such as we have in dead proteid. Starting with formic aldehyde Loew and Bokorny give a schema according to which there might be constructed a living molecule containing the requisite aldehyde and amido-groups; thus:

$$4HCOH + H_3N = C_4H_7NO_2 + 2H_2O.$$

Formic   Ammonia.   Aspartic
aldehyde.   aldehyde.
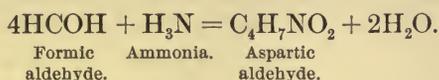
Further possible condensation of the aspartic aldehyde would give

$$3(C_4H_7NO_2) = C_{12}H_{17}N_3O_4 + 2H_2O,$$
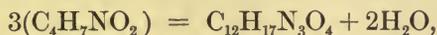
and by still further condensation with the addition of sulphur and some reduction we would get

$$6(C_{12}H_{17}N_3O_4) + 12H + H_2S = C_{72}H_{112}N_{18}SO_{22} + 2H_2O,$$

which represents, from their standpoint, the simplest expression of the structure of a proteid molecule possessing great lability and the power of further polymerization. Latham [1] proposes a theory which combines the ideas of Pflüger and of Loew. He suggests that the living molecule may be composed of a chain of cyan-alcohols united to a benzene nucleus. The cyan-alcohols are obtained by the union of an aldehyde with hydrocyanic acid; they contain, therefore, the labile-aldehyde grouping as well as the cyanogen nucleus to which Pflüger attributes such importance.

It has been assumed by many observers that the properties of living matter, as we recognize them, are not solely an outcome of the inner structure of the hypothetical living molecules. They believe that these latter units are fashioned into larger secondary units each of which is a definite aggregate of chemical molecules and possesses certain properties or reactions that depend upon the mode of arrangement. The idea is similar to that advanced by mineralogists to explain the structure of crystals. They suppose that the chemical molecules are arranged in larger or smaller groups to which the name "physical molecules" has been given. So in living protoplasm it may be that the smallest particles capable of exhibiting the essential properties of life are groups of ultimate molecules, in the chemical sense, having a definite arrangement and definite physical properties. These secondary units

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[1] *British Medical Journal*, 1886, p. 629.

of structure have been designated by various names such as "physiological molecules,"[1] "somacules,"[2] micellæ,[3] etc. Many facts, especially from the side of plant physiology, teach us that the physical constitution of protoplasm is probably of great importance in understanding its reaction to its environment. Microscopic analysis is insufficient to reveal the existence or character of these "physiological molecules," but it has abundantly shown that protoplasm has always a certain physical construction and is not merely a structureless fluid or semi-fluid mass. Most interesting in this connection are the recent views of Bütschli,[4] who believes that protoplasm is an aggregation of fluid vesicles filled with fluid, resembling somewhat the structure of a foam or the oily vesicles of an emulsion. He has in fact constructed an artificial foam of oil and potassium carbonate which not only gives many of the microscopic characters of protoplasm, but simulates the movements and currents observed in lower forms of life.

What has been said above may serve at least to indicate the prevalent physiological belief that the phenomena shown by living matter are in the main the result of the action of the known forms of energy upon a substance of a complex and unstable structure which possesses, moreover, a physical organization responsible for some of the peculiarities exhibited. In other words, the phenomena of life are referred to the physical and chemical structure of protoplasm and may be explained under the general physical and chemical laws which control the processes of inanimate nature. Just as in the case of dead organic or inorganic substances we attempt to explain the differences in properties between two substances by reference to the difference in chemical and physical structure between the two, so with regard to living matter the peculiar differences in properties which separate them from dead matter, or for that matter the differences which distinguish one form of living matter from another, must eventually depend upon the nature of the underlying physical and chemical structure.

In the early part of this century many prominent physiologists were still so overwhelmed with the mysteriousness of life that they took refuge in the hypothesis of a vital force or principle of life. By this term was meant a something of an unknown nature which controlled all the phenomena exhibited by living things. Even ordinary chemical compounds of a so-called organic nature were supposed to be formed under the influence of this force, and it was thought could not be produced otherwise. The error of this latter view has been demonstrated conclusively within recent years: many of the substances formed by the processes of plant and animal life are now easily produced within the laboratory by comparatively simple synthetic methods. By the distinguished labors of Emil Fischer[5] even the structure of carbohy-

[1] Meltzer: "Ueber die fundamentale Bedeutung der Erschütterung für die lebende Materie," *Zeitschrift für Biologie*, Bd. xxx., 1894.

[2] Foster: *Physiology* (Introduction).   [3] Nägeli: *Theorie der Gährung*, München, 1879.

[4] *Investigations on Microscopic Foams and on Protoplasm*, London, 1894; abstracted in *Science*, N. S., vol. ii. No. 52, 1895.

[5] *Die Chemie der Kohlenhydrate*, Berlin, 1894.

drate bodies has been determined, and bodies belonging to this group have been synthetically constructed in the laboratory.   Moreover, the work of Schützenberger and of Grimaux gives promise that before long, proteid bodies may be produced by similar methods.   Physiologists have shown, furthermore, that the digestion which takes place in the stomach or intestine may be effected also in test-tubes, and at the present day probably no one doubts that in the act of digestion we have to deal only with a series of chemical reactions which in time will be understood as clearly as it is possible to comprehend any form of chemical activity.   Indeed, the whole history of food in the body follows strictly the great mechanical laws of the conservation of matter and of energy which prevail outside the body.   No one disputes the proposition that the material of growth and of excretion comes entirely from the food.   It has been demonstrated with scientific exactness that the measurable energy given off from the body is all contained potentially within the food that is eaten,[1] and may be liberated outside the body by ordinary combustion.   Living things, so far as can be determined, can only transform matter and energy; they cannot create or destroy them, and in this respect they are like inanimate objects.   But, in spite of the triumphs which have followed the use of the experimental method in physiology, every one recognizes that our knowledge is as yet very incomplete.   Many important manifestations of life cannot be explained by reference to any of the known facts or laws of physics and chemistry, and in some cases these phenomena are seemingly removed from the field of experimental investigations.   As long as there is this residuum of mystery connected with any of the processes of life, it is but natural that there should be two points of view.   Most physiologists believe that as our knowledge and skill increase these mysteries will be explained, or rather will be referred to the same great final mysteries of the action of matter and energy under definite laws, under which we now classify the phenomena of lifeless matter.   Others, however, find the difficulties too great,—they perceive that the laws of physics and chemistry are not completely adequate at present to explain all the phenomena of life, and assume that they never will be. They suppose that there is something in activity in living matter which is not present in dead matter, and which for want of a better term may be designated as vital force or vital energy.   However this may be, it seems evident that a doctrine of this kind stifles inquiry.   Nothing is more certain than the fact that the great advances made in physiology during the last four decades are mainly owing to the abandonment of this idea of an unknown vital force and the determination on the part of experimenters to push mechanical explanations to their farthest limit.   There is no reason to-day to suppose that we have exhausted the results to be obtained by the application of the methods of physics and chemistry to the study of living things, and as a matter of fact the great bulk of physiological research is proceeding along these lines.   It is interesting, however, to stop for a moment to examine briefly some of the problems which as yet have escaped satisfactory solution by these methods.

[1] Rubner: *Zeitschrift für Biologie*, Bd. xxx. S. 73, 1894.

The phenomena of secretion and absorption form important parts of the digestive processes in higher animals, and without doubt are exhibited in a minor degree in the unicellular types. In the higher animals the secretions may be collected and analyzed and their composition be compared with that of the lymph or blood from which they are derived. It has been found that secretions may contain entirely new substances not found at all in the blood, as for example the mucin of saliva or the ferments and HCl of gastric juice; or, on the other hand, that they may contain substances which, although present in the blood, are found in much greater percentage amounts in the secretion—as, for instance, is the case with the urea eliminated in the urine. In the latter case we have an instance of the peculiar, almost purposeful, elective action of gland-cells of which many other examples might be given. With regard to the new material present in the secretions, it finds a sufficient general explanation in the theory that it arises from a metabolism of the protoplasmic material of the gland-cell. It offers, therefore, a purely chemical problem which may and probably will be worked out satisfactorily for each secretion. The selective power of gland-cells for particular constituents of the blood is a more difficult question. We find no exact parallel for this kind of action in chemical literature, but there can be no reasonable doubt that the phenomenon is essentially a chemical or physical reaction dependent upon an affinity of the secreted substance for some material within the gland-cell. We may indulge the hope that the details of the reaction will be discovered by more complete chemical and microscopical study of the structure of these cells. If in the meantime the act of selection is spoken of as a vital phenomenon it is not meant thereby that it is referred to the action of an unknown vital force, but only that it is a kind of action dependent upon the living structure of the cell-substance.

The act of absorption of digested products from the alimentary canal was for a time supposed to be explained completely by the laws of imbibition and diffusion. The epithelial lining and its basement membrane form a septum dividing the blood and lymph on the one side from the contents of the alimentary canal on the other. Inasmuch as the two liquids in question are of unequal composition with regard to certain constituents, a diffusion stream should be set up whereby the peptones, sugar, salts, etc. would pass from the liquid in the alimentary canal, where they exist in greater concentration, into the blood, where the concentration is less. Careful work of recent years has shown that the laws of diffusion are not adequate to explain fully the absorption that actually occurs; a more detailed account of the difficulties met with may be found in the section on Digestion and Nutrition. It has become customary to speak of absorption as caused in part by the physical laws of diffusion, and in part by the vital activity of the epithelial cells. It will be noticed that the vital property in this case is again a selective affinity for certain constituents similar to that which has been referred to in the act of secretion. The mere fact that the old mechanical theory has proved to be insufficient is in itself no reason for abandoning all hope of a satisfactory ex-

planation. Most physiologists unquestionably believe that further experimental work will bring this phenomenon out of its obscurity and show that it is explicable in terms of known physical and chemical forces acting through the peculiar substance of the absorptive cell.

The facts of heredity and consciousness offer difficulties of a much graver character. The function of reproduction is two-sided. In the first place there is an active multiplication of cells, beginning with the segmentation of the ovum into two blastomeres and continuing in the larger animals to the formation of an innumerable multitude of cellular units. In the second place there is present in the ovum a form-building power of such a character that the great complex of cells arising from it form not a heterogeneous mass, but a definite organism of the same structure, organ for organ and tissue for tissue, as the parent form. The ovum of a starfish develops into a starfish, the ovum of a dog into a dog, and the ovum of man into a human being. Herein lies the great problem of heredity. The mere multiplication of cells by direct or indirect division is not beyond the range of a conceivable mechanical explanation. Given the properties of assimilation and contractility it is possible that the act of cell-division may be traced to purely physical and chemical causes, and already cytological work is opening the way to credible hypotheses of this character. But the phenomena of heredity, on the other hand, are too complex and mysterious to justify any immediate expectation that they can be explained in terms of the known properties of matter. The crude theories of earlier times have not stood the test of investigation by modern methods, the microscopic anatomy of both ovum and sperm showing that they are to all appearances simple cells which exhibit no visible signs of the wonderful potentialities contained within them. Histological and experimental investigation has, however, cleared away some of the difficulties formerly surrounding the subject, for it has shown with a high degree of probability that the power of hereditary transmission resides in a particular substance in the nucleus, namely in the so-called chromatin material which forms the chromosomes. The fascinating observations which have led to this conclusion promise to open up a new field of experimentation and speculation. It seems to be possible to study heredity by accepted scientific methods, and we may therefore hope that in time more light will be thrown upon the conditions of its existence and possibly upon the nature of its activity.

In the facts of consciousness, lastly, we are confronted with a problem seemingly more difficult than heredity. In ourselves we recognize different states of consciousness following upon the physiological activity of certain parts of the central nervous system. We know, or think we know, that these so-called psychical states are correlated with changes in the protoplasmic material of the cortical cells of the cerebral hemispheres. When these cells are stimulated, psychical states result; when they are injured or removed, psychical activity is depressed or destroyed altogether according to the extent of the injury. From the physiological standpoint it would seem to be as justifiable to assert that consciousness is a property of the cortical nerve-cells

as it is to define contractility as a property of muscle-tissue.   But the short-
ening of a muscle is a physical phenomenon that can be observed with the
senses—be measured and theoretically explained in terms of the known prop-
erties of matter.   Psychical states are, however, removed from such methods of
study; they are subjective, and cannot be measured or weighed or otherwise esti-
mated with sufficient accuracy and completeness in terms of our units of energy
or matter.   There must be a causative connection between the objective changes
in the brain-cells and the corresponding states of consciousness, but the nature
of this connection remains hidden from us; and so hopeless does the problem
seem that some of our profoundest thinkers have not hesitated to assert that it
can never be solved.   Whether or not consciousness is possessed by all animals
it is impossible to say.   In ourselves we know that it exists, and we have
convincing evidence, from their actions, that it is possessed by many of the
higher animals.   But as we descend in the scale of animal forms the evidence
becomes less impressive.   It is true that even the simplest forms of animal
life exhibit reactions of an apparently purposeful character which some have
explained upon the simple assumption that these animals are endowed with
consciousness or a psychical power of some sort.   All such reactions, however,
may be explained, as in the case of reflex actions from the spinal cord, upon
purely mechanical principles, as the necessary response of a definite physical
or chemical mechanism to a definite stimulus.   To assume that in all cases of
this kind conscious processes are involved amounts to making psychical activity
one of the universal and primitive properties of protoplasm whether animal
or vegetable, and indeed by the same kind of reasoning there would seem to
be no logical objection to extending the property to all matter whether living
or dead.   All such views are of course purely speculative.   As a matter of
fact we have no means of proving or disproving, in a scientific sense, the exist-
ence of consciousness in lower forms of life.   To quote an appropriate remark
of Huxley's made in discussing this same point with reference to the crayfish,
" Nothing short of being a crayfish would give us positive assurance that such
an animal possesses consciousness."   The study of psychical states in our-
selves, for reasons which have been suggested above, does not usually form
a part of the science of physiology.   The matter has been referred to here
simply because consciousness is a fact which our science cannot as yet explain.

   So far, some of the broad principles of physiology have been considered—
principles which are applicable with more or less modification to all forms of
animal life and which make the basis of what is known as general physiology.
It must be borne in mind, however, that each particular organism possesses
a special physiology of its own, which consists in part in a study of the
properties exhibited by the particular kinds or variations of protoplasm
in each individual, and in large part also in a study of the various mechan-
isms existing in each animal.   In the higher animals, particularly, the com-
binations of various tissues and organs into complex mechanisms such as
those of respiration, circulation, digestion, or vision, differ more or less in
each group and to a minor extent in each individual of any one species.   It

follows, therefore, that each animal has a special physiology of its own, and in this sense we may speak of a special human physiology. It need scarcely be said that the special physiology of man is very imperfectly known. Books like the present one, which profess to treat of human physiology, contain in reality a large amount of general and special physiology which has been derived from the study of lower animal forms upon which exact experimentation is possible. Most of our fundamental knowledge of the physiology of the heart and of muscles and nerves has been derived from experiments upon frogs and similar animals, and much of our information concerning the mechanisms of circulation, digestion, etc. has been obtained from a study of other mammalian forms. We transfer this knowledge to the human being, and in general without serious error, since the connection between man and related mammalia is as close on the physiological as it is on the morphological side, and the fundamental or general physiology of the tissues seems to be everywhere the same. Gradually, however, the material for a genuine special human physiology is being acquired. In many directions special investigation upon man is possible; for instance, in the study of the localization of function in the cerebral cortex, or the details of body metabolism as obtained by examination of the excreta, or the peculiarities of vaso-motor regulation as revealed by the use of plethysmographic methods, or the physiological optics of the human eye. This special information, as rapidly as it is obtained, is incorporated into the text-books of human physiology, but the fact remains that the greater part of our so-called human physiology is founded upon experiments upon the lower animals.

Physiology as a science is confessedly very imperfect; it cannot compare in exactness with the sciences of physics and chemistry. This condition of affairs need excite no surprise when we remember the very wide field physiology attempts to cover, a field co-ordinate in extent with the physics as well as the chemistry of dead matter, and the enormous complexity and instability of the form of matter which it seeks to investigate. The progress of physiology is therefore comparatively slow. The present era seems to be one mainly of accumulation of reliable data derived from laborious experiments and observations. The synthesis of these facts into great laws or generalizations is a task for the future. Corresponding with the diversity of the problems to be solved we find that the methods employed in physiological research are manifold in character. Inasmuch as animal organisms are composed either of single cells or aggregates of cells, it follows that every anatomical detail with regard to the organization of the cell itself or the connection between different cells, and every advance in our knowledge of the arrangement of the tissues and organs which form the more complicated mechanisms, is of immediate value to physiology. The microscopic anatomy of the cell (a branch of histology which is frequently designated by the specific name of cytology), general histology, and gross anatomical dissection are therefore frequently employed in physiological investigations, and form what may be called the observational side of the science. On the other hand we have the experimental

methods, which seek to discover the properties and functional relationships of the tissues and organs by the use of direct experiments. These experiments may be of a surgical character, involving the extirpation or destruction or alteration of known parts by operations upon the living animal, or they may consist in the application of the accepted methods of physics and chemistry to the living organism. The physical methods include the study of the physical properties of living matter and the interpretation of its activity in terms of known physical laws, and also the use of various kinds of physical apparatus such as manometers, galvanometers, etc. for recording with accuracy the phenomena exhibited by living tissues. The chemical methods imply the application of the synthetic and analytic operations of chemistry to the study of the composition and structure of living matter and the products of its activity. The study of the subjective phenomena of conscious life—in fact, the whole question of the psychic aspects or properties of living matter—for reasons which have been mentioned is not usually included in the science of physiology, although strictly speaking it forms an integral part of the subject. This province of physiology has, however, been organized into a separate science, psychology, although the boundary line between psychology as it exists at present and the scientific physiology of the nervous system cannot always be sharply drawn.

It follows clearly enough from what has been said of the methods used in animal physiology that even an elementary acquaintance with the subject as a science requires some knowledge of general histology and anatomy, human as well as comparative, of physics, and of chemistry. When this preliminary training is lacking, physiology cannot be taught as a science; it becomes simply a heterogeneous mass of facts, and fails to accomplish its function as a preparation for the scientific study of medicine. The mere facts of physiology are valuable, indeed indispensable, as a basis for the study of the succeeding branches of the medical curriculum, but in addition the subject, properly taught, should impart a scientific discipline and an acquaintance with the possible methods of experimental medicine; for among the so-called scientific branches of medicine physiology is the most developed and the most exact, and serves as a type, so far as methods are concerned, to which the others must conform.

II. GENERAL PHYSIOLOGY OF MUSCLE AND NERVE.

A. INTRODUCTION.

It is seldom that the physical and chemical structure of a tissue, as revealed by the microscope and the most careful analysis, gives even a suggestion as to its function. No one would conclude from looking at a piece of beef, or even microscopically examining a muscle, that it had once been capable of motion, nor would the most exact statement of its chemical constitution give indication of such a form of activity. The most thorough histological and chemical examination of the bundle of fibres which compose a nerve would fail to suggest that a blow upon one end of it would cause to be transmitted to the other end an invisible change capable of exciting to action the cell with which the nerve communicated. To understand such a structure we must first learn the forms of activity of which the tissue is capable, the influences which excite it to action, and the conditions essential to its activity, and then seek an explanation of these facts in its physical and chemical structure.

Contractility.—One of the most striking properties of living matter is its power to move and to change its form. At times the movements occur apparently spontaneously, the exciting cause seeming to originate within the living substance, but more often the motions are developed in response to some external influence. This power finds its best expression in muscle-substance. In its resting form a muscle, such as the biceps, is elongated, and when it is excited to action it assumes a more spherical shape, *i. e.* shortens and thickens, whence it is said to have the property of *contractility*. It is the shortening, the contraction, of the muscle which enables it to perform its function of moving the parts to which it is attached, as the bones of the arm or leg, and of altering the size of the structures of which it forms a part, as the walls of the heart, intestine, or bladder. Ordinary muscle-substance is arranged in fine threads, each one of which is enveloped in a delicate membrane, the sarcolemma; these muscle-fibres can be compared to long sausages of microscopic proportions. A muscle is composed of a vast number of fibres arranged side by side in bundles, the whole being firmly bound together by connective tissue. Since isolated muscle-fibres have been seen under the microscope to contract, each fibre can be looked upon as containing true muscle-substance and being endowed with contractility. The movements of muscles are the resultant of the combined activity of the many microscopic fibres of which the muscles are composed.

The rate, extent, strength, and duration of muscular contractions are adapted

to the needs of the parts to be influenced, and it is found that the structure of the muscles differs according to the work which they have to perform. Thus we find two large classes of muscles : the one, like the muscles which move the bones, remarkable for the rapidity with which they change their form, but unsuited to long-continued action ; the other, occurring in the walls of the intestine, blood-vessels, bladder, etc., sluggish of movement, but possessing great endurance. The first of these, when examined with the microscope, is seen to be composed of bundles of fibres, which are transversely marked by alternating dark and light bands, and hence are called striated or striped muscles ; the other, though composed of fibres, shows no such cross markings, and therefore is known as smooth or non-striated muscle. Striated muscles are

FIG. 1.—Amœba proteus, magnified 200 times: *a*, endosarc ; *b*, simple pseudopodium ; *c*, ectosarc ; *d*, first stage in the growth of a pseudopodium ; *e*, pseudopodium a little older than *d* ; *f*, branched pseudopodium ; *g*, food-vacuole ; *h*, food-ball ; *i*, endoplast ; *k*, contractile vesicle (after Brooks : *Handbook of Invertebrate Zoology*).

often called voluntary, because most of them can be excited to action by the will, whereas non-striated muscles are termed involuntary, because in most cases they cannot be so controlled. Within these two large classes of muscles we find special forms presenting other, though lesser, differences in function and structure. The muscle of the heart, though striated, differs so much from other forms of striped muscle as almost to belong in a special class.

Since contractility is possessed by all forms of muscle-tissue, it is evident that it is independent of superficial structural differences. Nor is muscle the only substance possessing this property. Even isolated microscopic particles of living matter are capable of making movements, both spontaneously and when excited by external influences. As far back as 1755, Rosel von Rosenhof described the apparently spontaneous changes in form of a living organism composed of a single cell, a fresh-water amœba. Moreover, he noted that, if quiet, it could be excited to action by mechanical shocks.

The amœba (Fig. 1) is a little animal, of microscopic size, which is found in the ooze at the bottom of pools, or in the slime which clings to some of our fresh-water plants. Under the microscope it is seen to be composed of jelly-like, almost transparent matter, in which are a vast number of fine granules, a delicate tracery of finest fibrils, a small round body, called the nucleus or endoplast, a round hollow space termed the contractile vesicle, which is seen to change in size, appearing or disappearing from time to time, and small particles, which are bits of food or foreign bodies. In the resting state the body has a somewhat flattened, irregular form, which, if the slide on which it rests be kept warm, is found to alter from minute to minute. Little tongue-like projections, pseudopods (false feet), are protruded from the surface like feelers, and are then withdrawn, while others appear in new places. Evidently the little creature, though composed of a single cell, is endowed with life and has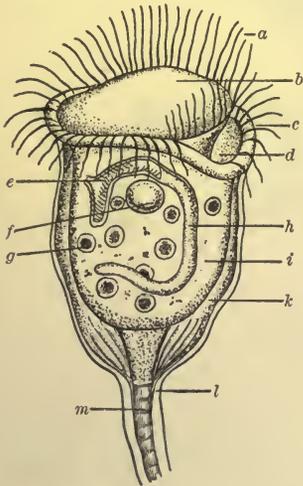 the power of making movements. Moreover, it may be seen to change its place, the method of locomotion being a peculiar one. One of the processes, or pseudopods, may be extended a considerable distance, and then, instead of being withdrawn, grow in size, while the body of the animal becomes correspondingly smaller; thus a transfer of material takes place, and this continues until the whole of the material of the cell has flowed over to the new place. This power of movement permits the animal to eat. If when moving over the slide it encounters suitable food material, a diatom for instance, it flows round it, engulfing it in its semifluid mass; and in a similar manner the animal gets rid of the useless substances which it may have surrounded, by flowing away from them. These movements may result from changes which have occurred within its own substance, and apparently independently of any external influence. On the other hand, if its body be disturbed by being touched, by an unusual temperature, by certain chemicals,

Fig. 2.—*Vorticella nebulifera,* × 600: *a,* cilia of ciliated disk; *b,* ciliated disk; *c,* peristome; *d,* vestibule; *e,* œsophagus; *f,* contractile vesicle; *g,* food-vacuoles; *h,* endoplast; *i,* endosarc; *k,* ectosarc; *l,* cuticle; *m,* axis of stem (after Brooks: *Handbook of Invertebrate Zoology*).

or by an electric shock, it replies by drawing in all of its pseudopods and assuming a contracted, ball form.

The movements of the leucocytes of the blood resemble in many respects those of the amœba.[1]

The property of contractility is possessed by a vast variety of unicellular structures in lower forms of animal life. Another example is the Vorticella (Fig. 2).

The vorticella, like the amœba, is a little animal which, although consisting of a single cell, possesses within its microscopic form all the physiological properties essential to life and the perpetuation of its species. It consists of a bell, with ciliated margin, borne upon a contractile stalk. If touched with a hair, or jarred, the cell rapidly contracts; the edge of the bell is drawn in so as to make the body nearly spherical, and the stalk is thrown into a spiral and drags the body back toward the point of attachment. The contraction is rapid; the relaxation, which comes when the irritation ceases, is gradual. An interesting account of the movements of *Vorticella gracilis* is given by Hodge and Aikins[2] under the title of "The Daily Life of a Protozoan."

Other examples of contractile power possessed by apparently simple organisms are to be found in the tentacles of Actiniæ, the surface sarcode of sponges, the chromatoblasts of Pleuronectidæ,[3] which are controlled by nerves and under the influence of light and darkness change their size and so alter the color of the skin, and the vast variety of ciliated forms, including spermatozoa, and some of the cells of mucous membranes.[4]

Irritability.—We have thus far referred to but one of the vital properties of protoplasm, viz. contractility. Another property intimately associated with it is *irritability.* Irritability is the property of living protoplasm which causes it to undergo characteristic chemical and physical changes when subjected to certain external influences called irritants. Muscle protoplasm is very irritable, and is easily excited to contraction by such irritants as electric shocks, mechanical blows, etc. The muscles which move the bones rarely, if ever, in a normal condition, exhibit spontaneous alterations in form, and cannot be said to possess automatic power. By *automatism* is meant that property of cell-protoplasm which enables it to become active as a result of changes which originate within itself, and independently of any external irritant. Examples of this power may perhaps be found in the movements of ciliated organisms and the infusoria. Possibly the rhythmic movements of heart muscle are of this nature. Still another property of protoplasm, closely allied to contractility and irritability, and possessed by muscle-substance, is conductivity.

Conductivity is the property which enables a substance, when excited in one part, to transmit the condition of activity throughout the irritable material. For example, an external influence capable of exciting an irritable muscle-fibre to contraction, although it may directly affect only a small part of

[1] An excellent description of these movements, accompanied by illustrations, is given in *Quain's Anatomy,* vol. i., pt. 2, pp. 174–179.

[2] Hodge and Aikins: *American Journal of Psychology,* 1895, vol. vi., No. 4, p. 524.

[3] Krukenberg: *Vergleichend-physiologische Vorträge,* 1886, Bd. i. p. 274.

[4] A careful study of the different forms of movement exhibited by simple organisms has been made by Engelmann: *Hermann's Handbuch der Physiologie,* 1879, Bd. i., Th. 1, p. 344.

the fibre, may indirectly influence the whole, because the condition of activity which it excites at the point of application is transmitted by the muscle-substance throughout the extent of the fibre.

Irritability and conductivity are not confined to contractile mechanism. They are possessed to a still higher degree by nervous tissues, which are not found to have the power of movement. The nervous system is composed of nerve-cells and nerve-fibres. The nerve-cells are located chiefly within the brain and spinal cord, a smaller number being found in the spinal ganglia and at special points along the course of certain nerve-fibres. The active part of the nerve-fibre is the axis-cylinder, which is an outgrowth from a nerve-cell, and which outside of the central nervous system acquires a delicate membranous sheath, the neurilemma, which invests it as the sarcolemma does the muscle-fibre. There are two classes of nerve-fibres, medullated and non-medullated, which are distinguished by the fact that the former has between the axis-cylinder and the neurilemma another covering composed of fatty material, called the medullary sheath, while in the latter this is absent. Just as it is the special function of the muscle-fibre to change its form when it is excited, so it is the special function of the nerve-fibre to transmit the condition of activity excited at one end throughout its length, and to awaken to action the cell with which it communicates. Nerve-fibres are the paths of communication between nerve-cells in the central nervous system, between sense-organs at the surface of the body and the nerve-cells, and between the nerve-cells and the muscle- and gland-cells. Nerve-fibres are distinguished as afferent and efferent, or centripetal and centrifugal, according as they carry impulses from the surface of the body inward or from the central nervous system outward. Further, they receive names according to the character of the activity which they excite : those which excite muscle-fibres to contract are called motor nerves; those distributed to the muscles in the walls of blood-vessels, vaso-motor; those which stimulate gland-cells to action, secretory; those which influence certain nerve-cells in the brain and so cause sensations, sensory. Still other names are given, as " trophic " to fibres which are supposed to have a nutritive function, and " inhibitory " to those which check the activities of various organs. The method of conduction is the same in all these cases, the result depending wholly on the organ stimulated.

Nerve-fibres do not run for any distance separately, but always in company with others. Thus large nerve-trunks may be formed, as in the case of the nerves to the limbs, in which afferent and efferent fibres run side by side, the whole being bound together into a compact bundle by connective tissue. The separate fibres, though thus grouped together, are anatomically and physiologically as distinct as the wires of an ocean cable; that these many strands are bound together is of anatomical interest, but has little physiological significance.

The active substance of the nerve-fibre does not show contractility, but this does not prevent it from being classed with other irritable forms of living cell-substance as protoplasm. In spite of differences in structure and composition, nerve protoplasm and muscle protoplasm are found to have many points of

resemblance. An explanation of the physiological resemblances may be found in their common ancestry. All the cells of the many structures of the animal body are descended from the two parent cells from which the animal is developed. The fertilized ovum divides, and two cells are formed, these new cells divide, and so the process continues, the developing cells through unknown causes becoming arranged to form more or less definite layers and groups, which by means of foldings and unequal growths develop into the various structures and organs of the fetus. At the same time that the division is going on, the total amount of material is increasing. Each of the cells absorbs and assimilates dead food-material, and this dead material is built into living substance. During this process of development and growth the cells of special tissues and organs acquire special anatomical and chemical characters. This development of specialized cells is termed cell-differentiation. Hand in hand with the anatomical and chemical differentiation goes a physiological differentiation. The protoplasm of each type of cell, while retaining the general characteristics of protoplasm, has certain physiological properties developed to a marked degree and other properties but little developed, or altogether lacking. The fertilized ovum does not have all the anatomical and chemical characteristics of all the cells which are descended from it, not at least in just the form in which they are possessed by these cells, and it cannot be assumed that its living substance possesses all the physiological properties which are owned by its descendants. Many of these properties it must have, for many of them are essential to the continuance of life of all active cells,—such as the power to take in, alter, and utilize materials which are suitable for the building up and repair of the cell-substance, the power of chemically changing materials possessing potential energy so that the form of actual energy which is essential to the performance of the work of the cell shall be liberated, and the power to give off the waste materials which result from chemical changes. The protoplasm of the ovum, to have these powers, has properties closely allied to absorption, digestion, assimilation, respiration, excretion ; and, in consideration of the special function of the ovum, we may add that it possesses the property of reproduction. The question of its possessing the characteristic properties of muscle and nerve protoplasm cannot be answered off-hand. Careful study, however, has shown the ovum of Hydra to possess irritability, conductivity, and contractility. It undergoes amœboid movements, as was first shown by Kleinenberg. Balfour,[1] in writing of the development of the ova of Tubularidæ, which is of a type similar to Hydra, says : " The mode of nutrition of the ovum may be very instructively studied in this type. The process is one of actual feeding, much as an amœba might feed on other organisms." Something similar seems to be true of the ova of echinodermata. During impregnation various movements are described implying the properties of irritability, conductivity, and contractility. Thus in the case of *Asterias glacialis*, when the head of the spermatozoon comes in contact with the mucilaginous covering of the ovum, "a prominence pointing toward the nearest spermatozoon now rises from the super-

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[1] *Comparative Embryology*, pp. 17, 29.

ficial layer of protoplasm of the egg and grows until it comes in contact with the nearest spermatozoon." " At the moment of contact between the spermatozoon and the egg, the outermost layer of protoplasm of the latter raises itself up as a distinct membrane, which separates from the egg and prevents the entrance of other spermatozoa." Some of the eggs of arthropods and other forms have likewise been observed to undergo amœboid movements as a result of the physiological stimulus given by the spermatozoon.[1]

Although irritability and contractility of the ovum have thus far been made out in but few forms, it is probable that they play an important part in all during fertilization and division. It would seem, then, that the ovum has all the principal properties which we ascribe to cell-protoplasm, and that these properties are inherited more or less completely developed by the many forms of cells descended from it. The protoplasm of specialized cells, in spite of their differences in structure, still retains its protoplasmic nature. Undoubtedly structural peculiarities are intimately related to specialized functions,—the striped muscle, for example, is especially adapted for rapid movements, and the nerve-fibre is remarkable for its power of conduction.

Physiological methods for the examination of individual cells are as yet in their infancy, and we must, for the most part, be content to study the functional activity of cells by observing the combined action of many cells of the same kind.

B. Irritability of Muscle and Nerve.

Irritability is the property of living protoplasm which causes it to undergo characteristic physical and chemical changes when it is subjected to certain influences, called irritants, or stimuli. By an irritant is meant an external influence which, when applied to living protoplasm, as of a nerve or muscle, excites it to action. Irritants may be roughly classed as mechanical, chemical, thermal, and electrical. The normal physiological stimulus is developed within some of the nervous mechanisms of the body as the result of the activity of the nerve-protoplasm, this having been excited as a rule by some form of irritant. The degree of irritability of a given form of protoplasm is measured by the amount of activity which it displays in response to a definite irritant, or by the minimal amount of irritation required to excite it to action. If the irritant be applied directly to a muscle, the height to which the muscle contracts and raises a given weight may be taken as an indication of its activity. As the nerve gives no visible evidence of activity, the effect of the irritant upon it is usually estimated by the extent to which the organ stimulated by the nerve reacts ; in the case of motor nerves, the strength of the contraction of the corresponding muscle is taken as an index.

To determine the exact relation of an irritant to its irritating effect we should be able to accurately measure them. This we cannot do. We are unable to state in irritation-units the relative value of different kinds of irritants. Even

[1] Korschelt: *Zoologischer Jahrbuch*, 1891, Anat. Abtheil., Bd. iv., Heft 1, p. 1. Hertwig: *Morphologische Jahrbuch*, 1876, Bd. 1. Herbst: *Biologische Centralblatt*, 1891, xiii. p. 22.

if we could accurately estimate the amount of energy which each form of irritant can expend in irritation, we should have only one of the many factors which determine its efficiency. It is equally difficult to compare the irritating effect of irritants upon different forms of protoplasm; *e. g.* we cannot state what degree of activity of a nerve-fibre corresponds to a certain amount of activity in a muscle-fibre. In spite of the lack of exact quantitative measurements, we have gained a clear idea of the way different forms of irritants act when applied to nerves and muscles in certain ways, and have learned to control the methods of excitation sufficiently to permit the influences which alter the irritability of nerves and muscles to show themselves. The effect of irritants can best be studied upon the nerves and muscles of cold-blooded animals, because these retain their vitality and irritability for a considerable time after they have been separated from the rest of the body. It is a common observation of country folk that the body of a snake remains alive for a long time after the head has been crushed, while the body of a chicken loses all signs of life in a comparatively short time after it has been decapitated. More careful examination would show that in neither case do all parts of the body die simultaneously. Each of the myriad cells has a life of its own, which it loses sooner or later according to its nature and to the alterations to which it is subjected by the fatal change. The cells of cold-blooded animals, as the snake and frog, are much more resistant than those of warm-blooded animals, because the vital processes within the cells are less active, and the chemical changes which precede and lead to the death of the part occur more slowly. For instance, the nerves and muscles of a frog remain irritable for many hours, or even days, after the animal has been killed and they have been removed from the body. This fact is of the greatest use to the student. It enables him to study the nerve or muscle by itself, and under such artificial conditions as he cares to employ. Experience shows that the facts learned from the study of the isolated nerve and muscle hold good, with but slight modification, for the nerves and muscles when in the normal body. Moreover, it has been found that the nerves and muscles of warm-blooded animals, and even man, resemble physiologically as well as anatomically those of the frog. The correspondence is by no means complete, but it is so great as to make the facts discovered by a study of the nerves and muscles of the frog of the utmost importance to us. We are driven to such sources of information because of the great difficulty of keeping the muscles of warm-blooded animals alive and in a normal condition after removal from the circulation.

Irritability of Nerves.—The following preparation suffices to illustrate the more striking effects of irritants upon a nerve. A frog is rapidly killed, and then the sciatic nerve is cut high up in the thigh and dissected out from its groove, the branches going to the thigh-muscles being divided. The leg is then cut through just above the knee. This gives a preparation consisting of the uninjured lower leg and foot, and the carefully prepared nerve supplying the muscles of these parts. The leg may be placed foot upward, and fastened in this position by a clamp which grasps the bones at the knee, the clamp

being supported by an upright (see Fig. 3). This preparation can then be subjected to a variety of tests.

Mechanical Irritation.—If the nerve be cut, pinched, suddenly stretched, or subjected to a blow, the muscles of the leg will contract and the foot will be quickly moved.
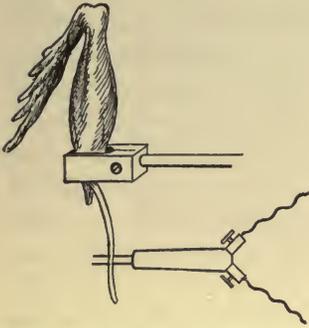
Chemical Irritation.—If acid, alkalies, various salts, glycerin, or some other chemical substances be placed upon the nerve, the muscles of the leg begin to twitch irregularly, and as the chemical enters more and more deeply into the nerve the movements will become more and more marked, until finally all the muscles are actively contracted and the foot is held straight up.

FIG. 3.—Experiment for determining the irritability of nerves.

Thermal Irritation.—If a hot iron, or the flame of a match, be applied to the nerve, a condition of activity will be developed in the rapidly heated nerve-fibres, and be responded to by more or less vigorous muscular contractions.

Electrical Irritation.—If the wires connected with the two poles of a galvanic cell, static machine, or induction apparatus be brought in contact with the nerve, the muscles will twitch each time there is a sudden change in potential.

More exact statements with reference to these different forms of irritation will be given later. By all these methods the nerve was excited by irritants applied to it from without, and the muscle was excited to action by the physiological stimulus coming to it from the excited nerve. The irritant produced no visible change in the nerve, but the movement of the muscles was an evidence that the nerve had undergone a change at the point of stimulation, and that the active state thus induced had been transmitted through the length of the nerve, and had been sufficiently marked to stimulate the muscle to contraction. This condition of activity which was transmitted along the nerve is called the nerve-impulse.

Independent Irritability of Muscle.—In the above instances the irritants were applied to the nerve, and the muscle was indirectly stimulated. Muscle protoplasm, like nerve protoplasm, may be directly excited to action by various forms of irritants. A nerve after entering a muscle branches freely, and the nerve-fibres are distributed quite generally through the muscle. An irritant, if directly applied to muscle, would probably excite the nerve-fibres present as well as the muscle-fibres, and to obtain proof of independent irritability of muscle-substance it would be necessary to prevent the nerves from stimulating the muscle. This can be done by paralyzing the nerve-endings with curare.

Curare, the South American arrow-poison, is used by the Indians in hunting. The bird shot by these poisoned arrows gradually becomes paralyzed, and, losing power to move its muscles, is easily captured. The following experiment reveals the method of the action of this drug, and at the same

time shows, first, that the muscle protoplasm can be irritated directly, and secondly, that the nerves do not communicate directly with the muscles, but stimulate them through the agency of terminal end-organs, called *motor end-plates.*[1]

Curare Experiment.—Rapidly destroy the brain of a frog with a slightly curved, blunt needle, and, to prevent hemorrhage, plug the wound by thrusting a pointed match through the foramen magnum into the brain-cavity. Expose the sciatic nerve of the left thigh, carefully pass a ligature under it, and tie the ligature tightly about all the tissues of the thigh excepting the nerve, thus cutting off the circulation from all the leg below the ligature without injury to the nerve. Inject into the dorsal lymph-sac or the abdominal cavity a few drops of a 2 per cent. solution of curare. In from twenty to forty minutes the drug will have reached the general circulation and produced its effect.

Although the brain has been destroyed and the frog is incapable of having sensation, it will be found that muscular movements will be made if the skin be pinched soon after the drug has been given. These are reflex movements, and are due to excitation of the spinal cord by the nerves connected with the skin. As the paralyzing action of the drug progresses, these reflex actions become feebler and feebler until altogether lost in the parts exposed to the drug, although they may still be shown by the parts from which the drug has been excluded. The condition of the nerves and muscles can be examined as soon as reflex movements of the poisoned parts cease.

To ascertain the action of the poison, expose the nerves of the two legs, either high up in the thigh or inside the abdominal cavity, where they have been subjected to the poison, and test their irritability by exciting them with electric shocks. Stimulation of the motor nerve of the right leg (*a*, Fig. 4) causes no contraction of the muscles of that leg, while stimulation of the motor nerve of the left leg (*b*), results in active movements of the muscles of that leg. The response of the left leg shows that nerve-trunks are not injured by the poison, and that the paralysis of the right leg must find some other explanation. On testing the muscles it is found that they are irritable and contract when directly stimulated. Since neither nerve-trunks nor muscles are poisoned, it is necessary to assume that the cause of the paralysis is something which prevents the nerve-impulse from passing from the nerve to the muscle. Microscopic examination shows that the nerve-fibre does not communicate directly with the muscle-fibre, but ends inside the sarcolemma in an organ which is called the motor end-plate. It appears that the nerve acts on the muscle through this organ, and its failure to act on the side which was exposed to the curare was because the end-plate had been paralyzed by the drug. By the use of curare, therefore, we are enabled to prevent the nerve-impulse from reaching the muscles, and, when we have done this, we find that the muscle is still able to respond to direct excitation with all forms of irritants, viz.

[1] Ch. Bernard: "Analyse physiologique des Propriétés des Systèmes musculaires et nerveux au moyen du Curare," *Comptes-rendus*, 1856, p. 825. Kölliker: "Physiologische Untersuchungen über den Wirkungen einiger Gifte," *Archiv für pathologische Anatomie*, 1856.

electrical, mechanical, thermal, and chemical. Evidently the muscle-proto-plasm is irritable and is capable of developing a contraction independently of the nerves.

Other Proofs that the Muscle-protoplasm can be Directly Irritated.—Muscles with long parallel fibres, such as the sartorius of the frog, contain no nerves at their extremities, the nerve-fibres joining the muscle-fibres at some little distance from their ends. The tip of such a muscle, where no nerve-fibres can be discovered by the most careful microscopical exam-ination, is found to be irritable. The fact that in some of the lower animals there are simple forms of contrac-tile tissue in which nerves cannot be discovered, and which are irritable, is interesting as corroborative evi-dence, although it is not a proof, of the independent irritability of a highly differentiated tissue such as striated muscle. Another similar piece of evidence is to be found in the fact that the heart of the embryo beats rhythmically before nerve appears to have been developed. A proof can be found in the observation that if a nerve be cut it begins to undergo degenera-tion and loses its irritability and conductivity in four or five days, and the excitation of such a nerve has no effect upon the muscle although direct stimulation of the muscle itself is followed by contraction. As degeneration involves not only the whole course of the nerve, but also the nerve end-plates, the contraction must be attributed to the irritability of the muscle-substance. Another point of interest in this connection is the behavior of a dying muscle. If it be struck, instead of contracting as a whole it contracts at the place where it was irritated, the drawing together of the fibres at the part forming a local swelling, or welt.
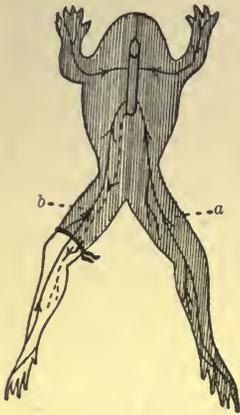
Fig. 4.—Curare experiment: the shaded parts show the re-gion of the body to which the drug had access; the unshaded part, the portion which was protected by the ligature from the action of the drug. The unbroken lines represent the sensory nerves which carry sensory impulses from the skin to the central nerv-ous system; the broken lines indicate the motor nerves, which carry motor impulses from the central nervous sys-tem out to the muscles (after Lauder Brunton: *Pharmacol-ogy, Therapeutics, and Materia Medica*).

If such a muscle be stroked, a wave of contraction spreads over it, following the instrument, instead of extending, as under normal conditions, by means of the excited nerve-fibres to other parts. Under these circumstances the circum-scribed contraction would seem to show that the nerves had lost their irrita-bility, or that the nerve-ends no longer transmitted the stimulus to the muscle, and the response was due to the direct excitation of the dying muscle-fibres. This phenomenon is known as an idiomuscular contraction.

CONDITIONS WHICH DETERMINE THE EFFECT OF EXCITATION.

The result of the irritation of nerve and muscle is dependent on two sets of conditions—namely, (1) Conditions which determine the irritability; (2) Conditions which determine the efficiency of the irritant.

It will be necessary for us to study the second set of conditions first,—for,

before we can judge of the irritability and the effect of various influences upon it, we must consider how far the activity of the nerve and muscle is dependent on the character, strength, and method of application of the irritant.

Conditions which Determine the Efficiency of Irritants.—Some of these conditions can be best studied on nerves, while others are more apparent in their effects on muscles. The most useful irritant for purposes of study is the electric current. Mechanical, thermal, and chemical irritants are likely to injure the tissue, and are not manageable, whereas electricity, if not too strong, can be applied again and again without producing any permanent alteration, and can be accurately graded as to strength, place, time, and duration of application, etc. Of course the results obtained by the use of a given irritant cannot be accepted for others until verified. The conditions which determine the effectiveness of the electric current as an irritant may be classed as follows:

(*a*) The rate at which the intensity changes.
(*b*) The strength of current.
(*c*) The density of current.
(*d*) The duration of application.
(*e*) The angle of application.
(*f*) The direction of flow.

Irritating Effect of the Electric Current.—Galvani, in seeking to find the effect of atmospheric electricity upon the animal body, suspended frogs by copper wires from an iron balcony, and observed the remarkable fact, that when the wind blew the legs against the balcony the muscles of the frogs twitched. He repeated the experiment in his laboratory, and concluded that the frogs had been excited to action by electric currents developed within themselves; he looked upon the metals which he had used merely as conductors for this current. Volta, Professor of Natural Philosophy at Pavia, repeated Galvani's experiment, and concluded that there had been an electric current developed from the contact of the dissimilar metals with the moist tissues of the frog. In accordance with this idea he constructed the voltaic pile, and this was the starting-point of the electric science of to-day.

Although it is true that, under certain conditions, differences in electric potential sufficient to excite muscles to contraction can be developed in the animal body, the contractions of the frog's leg which Galvani observed were due to the metals which he employed. The experiment can be easily performed by connecting a bit of zinc to a piece of curved copper wire, and bringing the two ends of the arc against the moist nerve and muscle of a frog. A stronger and more efficient shock can be obtained from a Daniell or some other voltaic cell.

A Daniell cell (Fig. 5) is composed of a zinc and copper plate, the former dipping into dilute sulphuric acid, the latter into a strong copper-sulphate solution. Although gravity will keep these liquids separated, if the cell is to be moved about it is better to enclose one of them in a porous cup. A common form of cell consists of a glass jar, in the middle of which is a porous cup; outside the cup is the sulphuric acid and the

zinc plate, and inside the cup is the copper sulphate solution and the copper plate. The zinc plate is acted upon by the sulphuric acid, and, as a result of the chemical change, a difference of electric potential is set up between the metals, so that if the zinc and copper be connected by a piece of metal, what we call an electric current flows from the zinc to the copper inside the cell, and from the copper to the zinc outside the cell. The zinc plate, being the seat of the chemical change, is called the positive plate, and the copper the negative plate. Several such cells may be connected together to form a battery, each cell adding to the electro-motive force, and hence to the strength of the current. As the current is always considered to flow from + to —, we call the end of the wire connected with the copper (negative plate) the positive pole, or *anode*, and the end of the wire connected with the zinc (positive plate) the negative pole, or *kathode*. If one of these wires be touched to a nerve, under ordinary circumstances no effect is produced; but when the other wire is likewise brought in contact with the nerve, the moist tissues of the nerve form a conductor, complete the circuit, and an electric current at once flows through the nerve from the anode to the kathode. The effect of the sudden flow of electricity into the nerve is to give it a shock—as we say, it irritates the nerve—and the muscle which the nerve controls is seen to contract.
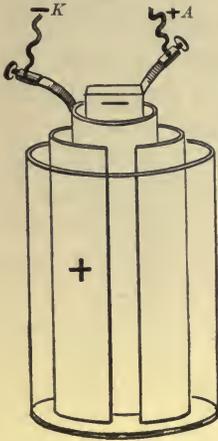
FIG. 5.—Daniell cell.

In the place of using ordinary wires for applying the electricity, we use electrodes. These are practically the same thing, but have insulated handles, and have a form better suited to stimulate nerves or other tissues. The two wires may be held in two different
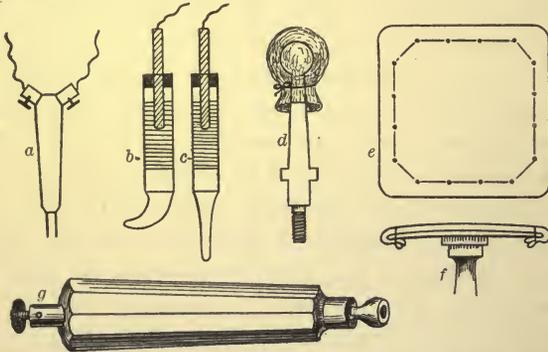
FIG. 6.—*a*, Ordinary electrode for exciting exposed nerves and muscles, consisting of two wires enclosed, except at their extremities, in a handle of non-conducting material; *b, c*, non-polarizable electrodes. When metals come in contact with moist tissues a galvanic action is likely to occur and polarizing currents to be formed. These extra currents would complicate or interfere with the results of many forms of experiment, and they are avoided by the use of non-polarizable electrodes. A simple form consists of a short glass tube, at one end of which is a plug of china clay mixed with a 0.6 per cent. solution of sodium chloride, and at the other end a cork through which an amalgamated zinc rod is thrust. The zinc rod dips into a saturated solution of zinc sulphate, which is in contact with the clay. The clay plugs touch the tissue to be excited, and the current passes from the zinc rods through the zinc-sulphate and sodium-chloride solutions in the clay to the tissues; *d–f*, electrodes for exciting human nerves and muscles through the skin (after Erb): these may be of various forms and sizes, and are arranged to screw into handles (*g*), to which the wires are attached; they are usually made of brass and covered with sponge or other absorbent material wet with salt-solution. The smaller electrodes are used when a dense, well-localized stream is required, and the larger electrodes when little action is wished and it is of advantage to have the stream diffuse.

handles, in which case we speak of the positive and negative electrodes, or the anode and the kathode, or they may be held in the same handle (Fig. 6).

Keys.—It is not as convenient to stimulate a nerve by touching it with the electrodes as

it is to place it upon the electrodes and close the connection between the zinc and copper at some other part of the circuit; this may be done by what is called a key. Any mechanism which can be used to complete the circuit could receive this name, and there are a number of convenient forms. The one most used by physiologists is that devised by Du Bois-Reymond, and which bears his name (see Fig. 7). This has the advantage of being capable of being used in two different ways—one simply as a means to close the circuit, and the other to short-circuit the current. These two methods are shown in Figure 8.
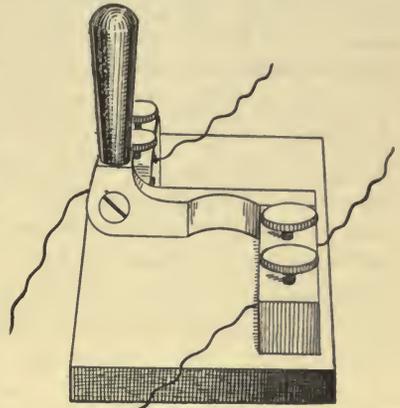
By the former method the key supplies a movable piece of metal by which contact between the two ends of the wires may be made as in *a* (Fig. 8), or broken as in *b*, and the current be sent through the nerve, or prevented from entering it. By the latter method the battery is all the time connected with the electrodes, and the key acts as a movable

FIG. 7.—Electric key.

bridge between the wires, and when closed gives a path of slight resistance by which the current can return to the battery without passing through the nerve. The current always takes the path of least resistance, and so, if the key be closed as in *c*, all the current will pass through the key and none will go to the nerve, which has a high resistance, whereas if the key be opened as in *d*, the bridge being removed, all the current will go through the nerve. It is often better to let the cell or battery work a short time and to get its full strength before letting the current enter the nerve, and the short-circuiting key permits of this. Moreover, there are times when a nerve may be stimulated if connected
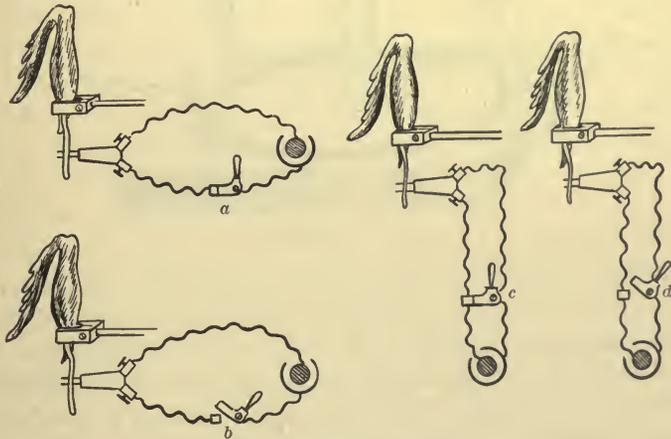
FIG. 8.—Electric circuiting.

with the source of electricity by only one wire, the circuit being completed through the earth; when the nerve is so excited, it is called unipolar stimulation; this may be prevented by the short-circuiting key.

As has been said, a nerve is irritated if it be connected with a battery and an electric current suddenly passes through it. Unless the current be very strong the irritation is transient, however; the muscle connected with the

nerve gives a single twitch at the moment that the current enters the nerve, and then remains quiet; and thus we meet with the remarkable fact that an electric current, though irritating a nerve at the moment that it enters it, can flow through the nerve continuously without exciting it. Further, although the current while flowing through the nerve does not excite it, a sudden withdrawal of the current from the nerve irritates it, and causes the muscle connected with it to contract. It is our custom to speak of closing, or making, the circuit when we complete the circuit and let the current flow through the nerve, and of opening, or breaking, the circuit when we withdraw the current from the nerve. Since the closing of the circuit acts as a sudden irritant to the nerve, we speak of this irritant as a "making" or "closing" shock, and the corresponding contraction of the muscles as a making or closing contraction; similarly we speak of the effect of opening the circuit as an "opening" or "breaking" shock, and the resulting contraction as an opening or breaking contraction. As we shall see later, the making contraction excited by the direct battery current is stronger than the breaking contraction : the explanation of this must be deferred (see page 53).

(a) *Effect of the Rate at which an Irritant is Applied, Illustrated by the Electric Current.*—As has been said, an electric current of constant medium strength
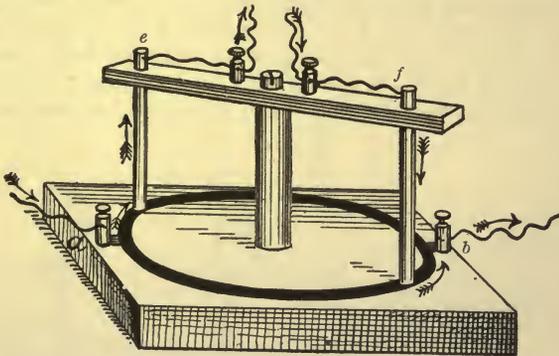
FIG. 9.—Rheonome.

does not irritate a nerve while flowing through it, but the nerve is irritated at the instant that the current enters it, and at the instant that the current leaves it. Is it the change of condition to which the nerve is subjected, or is it the suddenness of the change, which produces the excitation? Would it be possible to turn an electric current into a nerve and remove it from a nerve so slowly that it would not act as an irritant?

The experiment has been tried, and it has been found that if the nerve be subjected to an electric current the strength of which is increased or decreased very gradually, no change occurs in the nerve sufficient to cause a contraction of the muscle. In this experiment, instead of using the ordinary key, we close and open the circuit by means of a rheonome (see Fig. 9).

This instrument contains a fluid resistance, which can be altered at will, thereby permitting a greater or less strength of current to pass from the battery into the circuit

containing the nerve. The wires from the battery are connected with binding-posts, *a, b* (Fig. 9), at opposite sides of a circular groove containing a saturated solution of zinc sulphate. Strips of amalgamated zinc connect the binding-posts with the fluid, and so complete a circuit which offers much resistance to the passage of the current. From the centre of the block containing the groove rises an upright bearing a movable horizontal bar, from each extremity of which an amalgamated zinc rod, *e* and *f*, descends and dips into the zinc-sulphate solution. The zinc rods are connected with binding-posts on the movable bar, and from these wires pass to the electrodes on which the nerve rests. The bar revolves on a pivot on the top of the upright, and thus the zinc rods can be readily approached to or removed from the zinc strips, the poles of the battery. When the zinc rods hold a position midway between these poles, the current all passes by the way of the fluid. As the bar is turned, so as to bring the zinc rods nearer and nearer the two poles of the battery, the current divides, and more and more of it passes through the path of lessening resistance of which the nerve is a part. When the zinc rods are brought directly opposite the poles of the battery nearly all the current passes by the way of the nerve. If the bar be turned more or less rapidly, the current is thrown into, or withdrawn from, the nerve more or less quickly.

By this arrangement we can not only observe that the nerve fails to be irritated when the current is made to enter or leave it gradually, and when it is flowing continuously through it, but that sudden variations in the density of the current flowing through the nerve, such as are caused by quick movements of the bar, although they do not make or break the circuit, serve to excite. This experiment shows that electricity, as such, does not irritate a nerve, but that a sudden change in the density of the current, whether it be an increase or decrease, produces an alteration in the nerve-protoplasm which excites it to action and causes the development of what we call the nerve-impulse.

Du Bois-Reymond's Law.—Du Bois-Reymond formulated the following rule for the irritation of nerves by the electrical current: "It is not the absolute value of the current at each instant to which the motor nerve replies by a contraction of its muscle, but the alteration of this value from one moment to another; and, indeed, the excitation to movement which results from this change is greater the more rapidly it occurs by equal amounts, or the greater it is in a given time."

We shall have occasion to see that this rule has exceptions, or rather that there is an upper as well as lower limit to the rate of change of density of the electric current which is favorable to irritation.

Similar observations may be made with other forms of irritants. Pressure, if brought to bear on a nerve gradually enough, may be increased to the point of crushing it without causing sufficient irritation to excite the attached muscle to contract, although, as has been said, a very slight tap is capable of stimulating a nerve. Temperature, and various chemicals, likewise, must be so applied as to produce rapid alterations in the nerve-protoplasm in order to act as irritants. The same rule would seem to hold good for the nerve-cells of the central nervous system. It is a matter of daily experience that the nervous mechanisms through which sensory impressions are perceived are vigorously excited by sudden alterations in the intensity of stimuli reaching them, and but little affected by their continuous application; the withdrawal of light, a sudden

alteration of temperature, an unexpected noise, or the cessation of a monotonous sound, as exemplified by the common experience that a sleeper is awakened
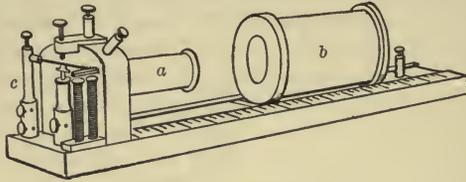

Fig. 10.—Induction apparatus: *a*, primary coil; *b*, secondary coil; *c*, the automatic interrupter.

when reading aloud abruptly ceases, attract the attention, although a continuous sensory irritation may be unnoticed. This physiological law of the nervous system would seem to have a psychological bearing as well.
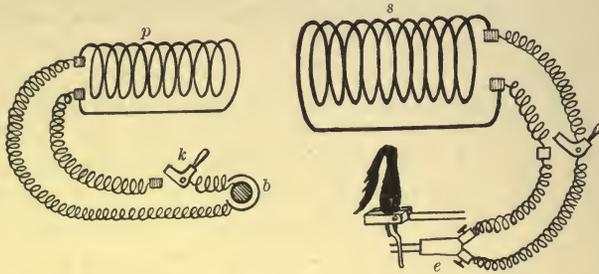

Fig. 11.—Schema of induction apparatus.

Irritating Effect of Induced Electric Currents.—Within certain limits, the more rapid the change in intensity of an electric current the greater its power to irritate. This probably accounts in part for the fact that the induced current is a more powerful irritant to nerves than the direct galvanic current. Induced currents are usually obtained by means of an induction apparatus (see Fig. 10).
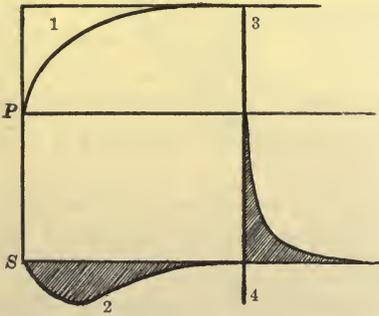
Fig. 12.—Schema of the relative intensity of induction currents (after Hermann, *Handbuch der Physiologie*, Bd. ii. S. 37): *P*, abscissa for the primary current; *S*, abscissa for the secondary current; 1, curve of the rise of intensity of the primary current when made; 2, curve of the rise and fall of intensity of the corresponding induced current; 3, curve of fall of the intensity of the primary current when it is broken; 4, curve of the rise and fall of intensity of the corresponding induced current.

The ordinary induction apparatus employed in the laboratory (see Fig. 11) consists of a coil of wire, *p*, which may be connected with the terminals of a battery, *b*, and a second coil, *s*, wholly independent of the first, which is connected with electrodes, *e*. At the instant that the key, *k*, in the primary circuit is closed, and the battery current enters the primary coil, an induced current is developed in the secondary coil, and the nerve resting on the electrodes is irritated. The induced current is of exceedingly short duration, suddenly rising to full intensity and falling to zero. As long as the battery current continues to flow constantly through the primary coil, there is no change in the electrical condition of the secondary coil, but at the instant the primary current is broken another induced current of short duration is set up in the secondary coil, and again the nerve receives a shock. The rise and

fall of the density of the current in the secondary coil is very rapid, and this rapid double change in density of the current causes the induction shock to be a very effective irritant. The break-ing induction shock, as we call that which is produced by breaking the primary current, is found to act more vigorously than the making shock, which is the reverse of what is found with direct battery currents. The cause of this lies in the nature of the apparatus. At the moment that the current begins to flow into the primary coil, it induces not only a current in the secondary coil, but also currents in the coils of wire of the primary coil. These extra induced currents in the primary coil have the opposite direction to the battery cur-rent and tend to oppose its entrance, and thereby to prevent it from immediately gain-ing its full intensity. This delay affects the development of the induced current in the secondary coil, causing it to be weaker and to have a slower rise and fall of intensity than would otherwise be the case. When the primary current is broken, on the other hand, there is no opposition to its cessation, and the current induced in the secondary coil is intense and has a rapid rise and fall. These differences are illustrated in Figure 12.

To accurately test the effect of the making and breaking induction shocks, it is necessary to record the reaction of the nerve; this can be done by record-ing the extent to which the corresponding muscle contracts in response to the stimulus which it receives from the nerve. In such an experiment it is customary to use what is known as a nerve-muscle preparation. The gas-trocnemius muscle and sciatic nerve of a frog, for instance, are carefully dissected out, the attachment of the muscle to the femur being preserved, and the bone being cut through at such a point that a sufficiently long piece of it shall be left to fasten in a clamp, and so support the muscle (see Fig. 13).
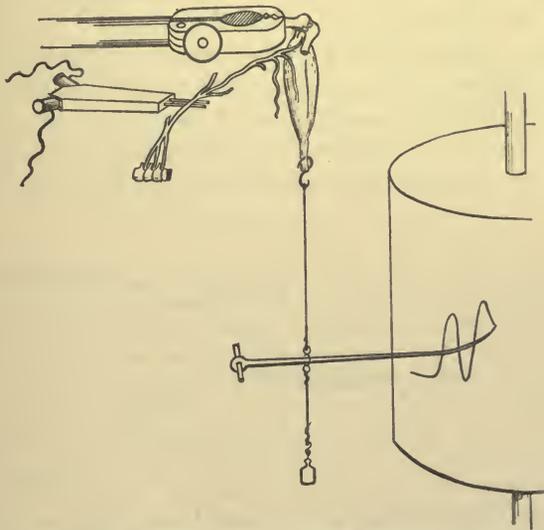
FIG. 13.—Method of recording muscular contraction.

The simplest method of recording the extent of the muscular contraction is to connect the muscle by means of a fine thread with a light lever, and let the point of the lever rest against a smooth surface covered with soot, so that when the muscle contracts it shall draw up the lever and trace a line of cor-responding length upon the blackened surface. The combination of instru-

4

ments employed to record the contraction of a muscle is called a *myograph*, and the record of the contraction is termed a *myogram*. If, when the muscle of a

FIG. 14.—Effect of making and breaking induction shocks.

nerve-muscle preparation is thus arranged to write its contractions, the nerve be irritated with alternating making and breaking induction shocks of medium strength, the muscle will make a series of movements, which, if the surface be moved past the writing-point a short distance after each contraction, will be pictured in the record as a row of alternating long and short lines, the records of the breaking contractions being higher than those of the making contractions (Fig. 14). Similar results are obtained if, instead of irritating the nerve, we irritate the curarized muscle directly.

Stimulating Effects of Making and Breaking the Direct Battery Current.— On account of the construction of the induction apparatus, breaking induction shocks are more effective stimuli than making induction shocks. The reverse is true of the stimulating effects which come from making and breaking the direct battery current. The excitation which results from sending a galvanic current into a nerve or muscle is stronger than that which is caused by the withdrawal of the current. This difference is due to the physiological alterations produced by the current as it flows through the irritable substance, and is without doubt closely associated with changes in the irritability which occur at the moment of the entrance and exit of the current.

The making contraction starts from the kathode, and the breaking contraction from the anode. The irritation process which results from making the current is developed at the kathode, and that which results from breaking the current is developed at the anode. This was first demonstrated on normal muscles by Von Bezold,[1] and has since been substantiated for nerves as well as muscles
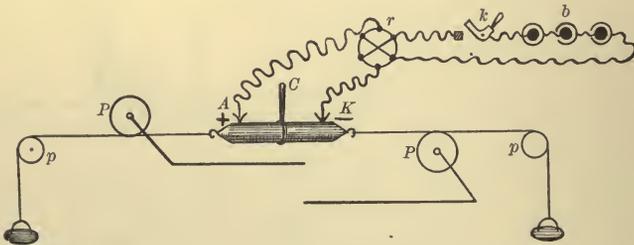

FIG. 15.—Schema of Hering's double myograph: *C*, clamp holding middle of muscle; *P,P*, pulleys to the axes of which the recording levers are attached; *p,p*, pulleys for the light weights which keep the muscle under slight tension; *A*, positive electrode; *K*, negative electrode; *r*, commutator for reversing the current; *k*, key; *b*, battery.

by the experiments of a great many observers. Perhaps the most striking demonstration is to be obtained by Engelmann's method. The positive and negative electrodes are applied to the two extremities of a long curarized sarto-

[1] *Untersuchungen über die elektrische Erregung von Muskeln und Nerven*, 1861.

rius muscle, which is clamped in the middle firmly enough to prevent the con-
tractions of one half from moving the other, but not enough to interfere with
the conduction-power of the tissue. The record of the contractions is best
obtained by the double myograph of Hering (Fig. 15), which permits the
recording levers attached to the two ends of the muscle to write directly under
each other, so that any difference in the beginning of the contraction of the
two halves of the muscle is immediately recognizable from the relative posi-
tions of the records of their contractions.

The current is applied to the two extremities of the muscle by non-polarizable electrodes.
In all experiments with the direct battery current it is essential to employ non-polarizable
electrodes. The form devised by Hering is very useful where the current has to be applied
directly to the muscle, because the two electrodes are hung from pivots in such a way that
they move with the movements of the muscle, and hence do not shift their position when
the muscle contracts. Some kind of apparatus has to be employed for quickly reversing
the direction of the current. A convenient in-
strument for this purpose is Pohl's mercury com-
mutator (Fig. 16). This instrument consists of
a block of insulating material in which are six
little cups containing mercury, which is in con-
nection with binding-posts on the sides of the
block. Two of the mercury cups on the opposite
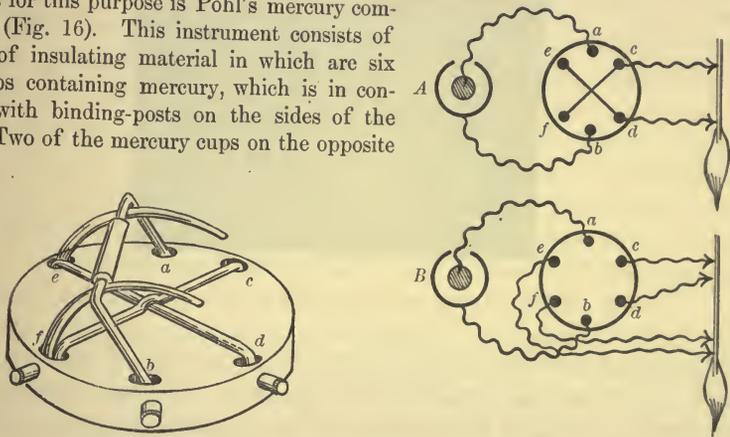
FIGS. 16, 17.—Pohl's mercury commutator.

sides of the block *a* and *b* (Fig. 17, *A*), are connected by wires with the battery; two others,
c and *d*, are connected with wires which pass to the electrodes; the remaining two on the
opposite side of the block, *e* and *f*, are joined by movable good conducting wires with the
cups *c* and *d* in such a way that *c* connects with *f*, and *d* with *e*. Two anchor-like pieces of
metal are connected by an insulated handle, and are so placed that the stocks of the anchors
dip into the mercury cups *a* and *b* (Fig. 16). The anchors can be rocked to one side or the
other, so that the ends of the curved arms shall dip into the cups *c* and *d* (in which case
cup *a* will be connected with cup *c*, and cup *b* with cup *d*), or so that the other ends of the
arms shall dip into cups *e* and *f* (in which case cup *a* will be connected with cup *e*, and by
means of the cross wire with cup *d*, and cup *b* will be connected with cup *f*, and by means
of the cross wire with cup *c*). By the arrangement shown in Fig. 17, *A* the current can
pass from the battery by way of *a* and *c* down the nerve, and by way of *d* and *b* back to
the battery; or it can pass from the battery by way of *a*, *e*, *d*, and in the reverse direction,
up the nerve and back to the battery, by way of *c*, *f*, *b*.

This commutator can be used in another way (see Fig. 17, *B*). If the battery be con-
nected with it as before, and the cross wires be removed, the current can be sent at will
into either one of two separate circuits. For instance, if the cups *c*, *d* be connected with
the electrodes on one part of the nerve, and the cups *e*, *f* with the electrodes on another

part, the anchors have only to be rocked to one side or the other to complete the commu-
nication between the battery and one or the other of these pairs of electrodes.

In experiments with the double myograph, in which the *making* of the
current is used to irritate, records are obtained such as are shown in Figure 18.
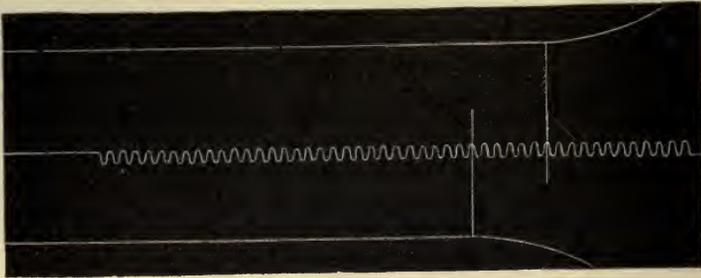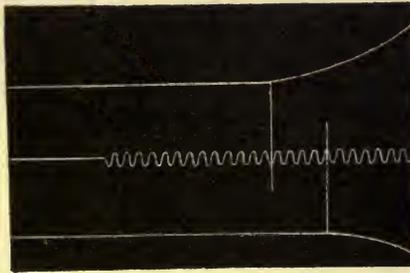
Fig. 18.—The making contraction starts at the kathode (after Biedermann).

In these records the beginning of the tuning-fork waves shows the moment
that the current was made and the irritation given. In the experiment from
which record *a* was taken the anode was at the knee-end of a curarized sartorius
muscle and the kathode at the pelvic end—*i. e.* the current was ascending
through the muscle. The lower of the two curves was that got from the
kathode half, the arrangement being that shown in Figure 15, and the lower
curve began before that got from the anode half; *i. e.* the contraction originated
at the kathode and spread thence over the muscle. In *b* the current was
reversed, and the upper curve was obtained from the kathode half and the
lower from the anode half; in this also the *kathode* end contracted first.
In the above experiments the making of the current was used to irritate,
and the muscular contraction began at the kathode; in experiments in which
the breaking of the current was employed the opposite was observed, the
anode end being seen to contract first, regardless of the direction of the cur-
rent.

If strong currents be used, the fleeting contractions which result from
opening and closing the current are followed by continued contractions, the
closing, Wundt's, and the opening, Ritter's tetanus, as they are called. These
continued contractions, which last for a considerable time, remain strictly
located at the region where they originate, and Engelmann proved by his

experiments that the tetanus which results from closing a strong current remains located at the kathode, and the tetanus following the opening of the current remains located at the anode.

The same is true of the nerve as of the muscle; the irritating process which is called out by the sudden entrance of a battery current into a nerve starts from the negative pole, the kathode, and spreads thence throughout the nerve, while the irritating process excited by the cessation of the flow of the current starts from the region of the positive pole, the anode, and spreads from that point throughout the nerve. A proof of this was obtained by Von Bezold, who observed the difference in the time between the moment of excitation and the beginning of the contraction of the muscle, when the nerve was excited by opening and by closing the current, with the anode next to the muscle, and with the kathode next to the muscle. He found the time to be longer when the current was closed if the kathode was the more distant, and to be longer when the current was opened if the anode was farther from the muscle. Evidently in the case of the nerve as of the muscle, the irritable substance subjected to the current is not all affected alike. The current does not set free the irritating process at every part of the nerve, but produces peculiar and different effects at the two poles, the change which occurs at the kathode when the current is closed being of a nature to cause the development of the excitatory process which awakens the closing contraction, and the change which occurs at the anode when the current is opened being such as to cause the development of the excitatory process which calls out the opening contraction.

Closing contractions are stronger than opening contractions. The irritation developed at the kathode is stronger than that developed at the anode. It is true of both striated and unstriated muscles that an efficient irritation can be developed at the kathode with a weaker irritant than at the anode. Moreover, a greater strength of current is required to produce opening than closing continued contractions.

The same may be said of nerves. If one applies a very weak battery current to the nerve of a nerve-muscle preparation, he notices when he closes the key a single slight contraction of the muscle, and when he opens the key, no effect. If he then increases the strength of the current very gradually, and tests the effects of the making and breaking of the current from time to time, he observes that each time the strength of the current is increased the closing contraction, which is due to irritation originating in the part of the nerve subject to the kathode, grows stronger, and finally contractions are also seen when the circuit is broken, the irritation process developed at the anode having become strong enough to excite the muscle. These opening contractions at first are weak, but gradually increase in strength, until with a medium strength of current vigorous contractions are seen to follow both opening and closing of the current. If the strength of the current be still further increased, it is found that either the closing or opening contraction begins to decrease in size, and if a very strong current be employed, the closing or opening con-

traction will be absent. It has been ascertained that the direction in which the current is flowing through the nerve determines which of these contractions shall cease to appear. The cause of this will be explained a little later.

(b) *Effect of Strength of Irritant.*—As a rule, the stronger an electric current the greater its irritating effect. This can be readily tested upon a nerve with the induction current, the strength of which can be varied at pleasure. The strength of the induced current obtained from a given apparatus depends upon the strength of the current in the primary coil, and on the distance of the secondary from the primary coil. In ordinary induction machines (see Fig. 10, p. 48) the secondary coil is arranged to slide in a groove, and can be easily approached to or removed from the primary coil, thus placing the coils of wire of the secondary coil more or less under the influence of the magnetic field about the primary coil. This permits the strength of the current to be graded at will. The strength of the induced current does not increase, however, in direct proportion to the nearness of the coils. As the secondary approaches the primary coil, the induced current increases in strength at first very slowly, and later more and more rapidly, reaching its greatest intensity when the secondary coil has been pushed over the primary.

The relation of the strength of a current to the irritating effect upon a nerve can be readily tested with such an induction apparatus. The secondary coils can be connected with a pair of electrodes on which the nerve of a nerve-muscle preparation rests (as in Fig. 11, page 48), and the muscle can be arranged to record the height of its contractions (as in Fig. 13, p. 49). The experiment can be begun by placing the secondary coil at such a distance from the primary that the making and breaking shocks are too feeble to have any effect upon the nerve. Then the secondary coil can be gradually approached to the primary, the primary current being made and broken at regular intervals. At a certain point the breaking shock will excite a very feeble contraction, the making shock producing no effect. If this contraction is barely sufficient to be recognized, we call it the minimal breaking contraction (see Fig. 19, *a*). In seeking the minimal contraction care must be taken not to excite the preparation at too short intervals of time, for, as we shall see, an irritation too slight to excite even a minimal contraction may, if repeated at short intervals, increase the irritability of the preparation and so become effective. By using a short-circuiting key in the secondary circuit we can cut out the making shocks, and test the effect of a further increase in the strength of the current by the response of the muscle to the breaking shocks. As the contractions become larger, care must be taken not to irritate the muscle too frequently, lest it be fatigued and so fail to give the normal response. As the current is strengthened the breaking contractions will become higher and higher until a point is reached beyond which the strength of the current may be increased to a considerable extent without any further heightening effect (Fig. 19, *b*). If the current be still further increased, this first maximum is succeeded by a still further growth in the height of the contractions, until finally

a second maximum (Fig. 19, *d*) is reached, beyond which no further increase is to be obtained, however much the current may be strengthened.[1]

FIG. 19.—Effect of increase of strength of current on the efficiency of breaking induction shocks (after Fick): *a*, minimal contraction; *b–c*, first maximum; *d–e*, second maximum.

If both the making and breaking contractions be recorded, inasmuch as the making shocks are weaker stimuli than the breaking (see p. 50), the making contractions do not appear until after the breaking contractions have acquired a considerable height. After the making minimal contraction has been obtained, the making contractions rapidly gain in height as the current is strengthened, and finally acquire the same height as the maximal breaking shocks.

The relation of the strength of the electric current to its irritating power can be demonstrated equally well by using the direct galvanic current. The strength of the galvanic current depends upon the character and number of the cells employed, and the total resistance in the circuit. The strength of the current can be easily varied by altering the resistance, and there are a number of forms of apparatus for this purpose.
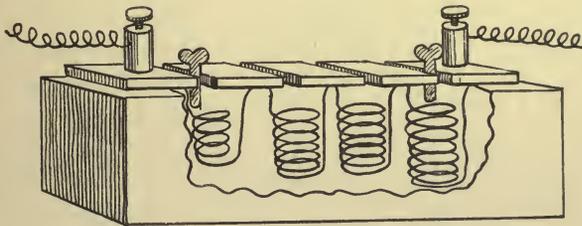
FIG. 20.—Rheostat.

A convenient instrument is the rheostat (Fig. 20). This is a box containing coils of wire of known resistance. These coils are connected with a series of heavy brass blocks on top of the box. The current enters the box by a binding-post attached to the first of the brass blocks and passes thence from block to block, by going through the coils of wire connecting them, until it reaches the binding-post at the other end of the series. The blocks can be also connected by good conducting brass plugs, which can be pushed in between them, and when this is done, as the current passes directly from block to block instead of going through the resistance coils beneath, the resistance is reduced to a corresponding amount.

Another method of altering the strength of the current flowing through the nerve is to employ some form of shunt to split the current so that only a part of it shall pass by way of the nerve. A current takes the path of least resist-

[1] Fick: *Untersuchungen über elektrische Nervenreizung*, Braunschweig, 1864.

ance, and if two paths are opened to it, more or less can be sent through one of them by decreasing or increasing the resistance in the other.

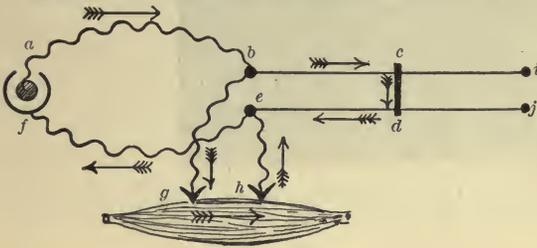A useful instrument for dividing the current is the rheocord. The schema given in Figure 21 illustrates the way in which it is used. The amount of current passing to the nerve will vary with the relative resistance in a, b, c, d, e, f, and in a, b, g, h, e, f. The bridge c, d can be slid along the fine German-silver wires b, i and e, j, and thus the resistance a, b, c, d, e, f, and the amount of current passing through the nerve, can be varied at pleasure.

FIG. 21.—Rheocord.

With such an arrangement we should find that the irritating effect of the current is largely dependent upon its strength. In the case of strong currents, however, the results may be complicated by alterations in the irritability and conductivity, which we will consider later. It is true also of other forms of irritants, and of muscles as of nerves, that the effect of stimulation, up to a certain limit, increases with the strength of the irritant.

(c) *Effect of Density of the Current.*—Although the strength of the current is an all-important factor in its excitatory action, the effectiveness of the current as an irritant depends very largely on the density of the stream. When the current enters into a conductor, it spreads widely through the conducting substance, and though the larger part of it takes the path of least resistance, which is usually the shortest path to the point of exit, many of the threads of current make a comparatively wide circuit to reach the outlet. If the conductor is equally good at all points, but is irregularly shaped, the density of the stream will be greatest where the diameter of the conductor is least. Thus it happens that if a current be made to flow from end to end of a muscle, like the sartorius of the frog, which is smaller at the knee end than at the pelvic end, the density of the current will be greater at the lower than at the upper end, and the irritating power of the current will be greater at the lower end.[1]

This question of the effect of the density of the current is important, as it helps to explain the peculiar reactions to the electric stream obtained when a current is applied under normal conditions to the human nerve.

(d) *Effect of the Duration of the Electric Current on its Power to Irritate Nerves and Muscles.*—As we have seen, a constant battery current, when flowing uninterruptedly through a motor nerve, does not ordinarily excite it; very slow variations in the strength of the current also fail to irritate; but rapid alterations in the strength, whether in the direction of increase or decrease, act as vigorous stimuli. For example, medullated nerves are irritated more vigorously by the rapid changes of intensity of induced currents than by the somewhat slower changes occurring at the make and break of battery currents. Within certain limits, at least, the more rapidly the intensity of the current

[1] Biedermann: *Elektrophysiologie*, 1895, Bd. i. p. 185.

changes, the greater the irritating effect upon nerves. Not all nerves, however, are equally susceptible to rapid alterations of the intensity of the current. Non-medullated nerves do not appear to react as readily as medullated to electric currents of short duration. For instance, the nerves of the claw muscles of the crab are not readily excited by induced currents, and respond better to the more prolonged influence of the closing and opening of battery currents.[1]

The question now arises, Is the reaction of muscles to electric currents the same as that of nerves? Experiment shows that muscles which have been removed from the action of nerves, by means of curare, differ from medullated nerves in that they are excited more vigorously by the opening and closing of battery currents than by making and breaking induction currents. The maximal contraction got on opening and closing a battery current is both higher and more prolonged than that to be obtained with a single induction shock. Unstriated muscles exhibit this difference to a still greater degree than striated muscle; they react well to the closing of battery currents of medium strength, provided these last some little time, but respond to induced currents only when they are very strong. Thus the unstriated muscle which closes the shell of some of the fresh-water mussels, as the Anodonta, gives larger and larger contractions as the duration of the current is increased from one-quarter of a second to three seconds. Much the same is true of the unstriated muscles of the ureters;[2] the battery current must remain closed quite a while for the closing contraction to be called out, the length of time depending upon the strength of the current; and induction shocks have little or no effect unless very strong. Such a comparison makes it evident that the duration of the current is an important element in the influence exerted by electric currents on various forms of protoplasm. Unstriated muscles require that the current shall last from one-quarter of a second to three seconds to produce maximum contractions. Striated muscles require that a current shall last 0.001 second (Fick), and even medullated nerves fail to react if the current lasts too short a time. Various forms of irritable tissue can be arranged in series according to their ability to respond to electric currents of short duration, viz. medullated nerves, non-medullated nerves, striated muscles, non-striated muscles, and the little-differentiated forms of protoplasm of many of the protozoa. On the other hand these tissues are found to respond in the reverse order to currents which are more prolonged and which change their intensity slowly. It would seem as if the less perfectly differentiated the form of protoplasm, the less its mobility and its susceptibity to passing influences.

The same form of tissue reacts differently in different animals. For instance, the sluggish striated muscles of the turtle do not respond as well to induced currents as the more rapid striated muscles of the frog. Further, the condition of the tissue at the time is found to have an influence on its irritability and its power to respond to stimuli of short duration. Von Kries reports that nerves, if cooled, react better to slow variations in the intensity of the electric current,

[1] Biedermann: *Elektrophysiologie*, 1895, Bd. ii. p. 546.
[2] Engelmann: *Pflüger's Archiv*, 1870, Bd. iii. p. 263.

and, if warmed, to rapid variations. Under pathological conditions the reaction of nerve and muscle to electric currents may become blunted, and, as the tissue degenerates, its power to respond to rapid changes of the electric current is lessened. If a nerve be cut, the part which is separated from the influence of the nerve-cells degenerates. The irritability at first increases and then very rapidly decreases, in from three to four days being wholly lost. As the nerve regenerates, the irritability is recovered very gradually, and the power to respond to the relatively prolonged action of mechanical stimuli is regained sooner than the ability to reply to changes as rapid as those of induced currents. Howell and Huber observed that regenerating nerve-fibres when they have reached the stage resembling embryonic fibres, *i. e.* are strands of protoplasm without axis-cylinders, fail to respond to induction currents, though they can be excited by mechanical stimuli. It was found that it is not until the axis-cylinder has grown down into the regenerating fibres that the nerve is capable of responding to induction shocks.

When human striated muscle undergoes degeneration as a result of an injury to its nerve, the degenerating muscle comes to resemble normal unstriated muscle in its reactions to electricity, responding feebly to induced currents, at a time when irritability to mechanical stimuli and to direct battery currents is even increased. This is used by clinicians as a means of diagnosis of the condition of the nerve and muscle.

From what has been said it is evident that the rule laid down by Du Bois-Reymond (see p. 47) must be modified in so far that there is for each tissue a limit to the rate at which a change of intensity of the electric current acts as an irritant. An extreme illustration of this may be found in the astonishing fact lately published by Tessla, that although in general alternating dynamo currents are very deadly, a current of even high voltage may be passed through the human body with impunity, provided that the rate of alternations be sufficiently rapid.

(*e*) *Effect of the Angle at which the Current Enters and Leaves the Muscle and Nerve.*—The angle at which the current acts on the muscle-fibre has been found to have a bearing upon its power to stimulate. Leicher[1] succeeded in obtaining definite experimental evidence that when the current is so sent through a muscle as to cross it at right angles to its fibres it has no irritating effect, and that its power to stimulate increases as the angle at which the threads of current strike the muscle-fibres decreases, being greatest when the current passes longitudinally through the fibres.

Similarly, it was found by Albrecht and Meyer[2] that the irritating effect of the electric current is most active when it flows longitudinally through the nerve, and that it is altogether absent when it flows transversely through it. This view is doubted by some observers, who would attribute the difference observed to differences in the electrical resistance. It is true that the resistance to cross transmission is greater than to longitudinal transmission, but it

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[1] *Untersuchungen aus dem physiologischen Institut der Universität Halle,* Heft i. p. 5.
[2] *Pflüger's Archiv,* 1880, Bd. xxi. p. 462.

is not likely that this difference suffices to explain the lack of response to currents applied at right angles to the nerve-axis.

Relative Efficacy of the above Conditions upon the Irritating Power of the Electric Current.—When a current is applied to an irritable part of a nerve or muscle at an angle suitable to excitation, the stimulating effect of the current depends upon the rate at which its intensity is changed, the strength and density of the current, *i. e.* its intensity, and the duration of the current.

Fick[1] gives the following schema (Fig. 22) for the different ways in which the intensity of the electric current may be varied, and compares the effects of these different methods of application of the current. It must be remembered that a decrease of intensity acts no less than an increase to produce
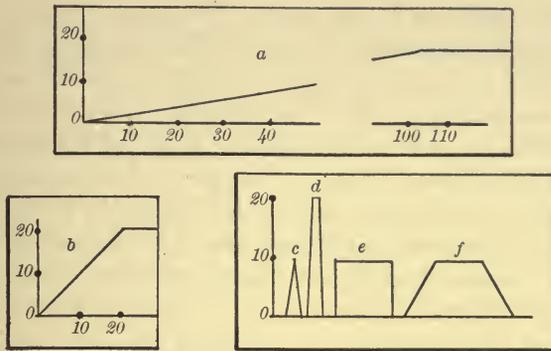
FIG. 22.—Schema of relation of the method of application of the electric current to the irritating effect.

excitation. In the above schema the abscissa represents the time, and the ordinates the strength, of the current. Suppose the rise of intensity has a form such as is represented in *a*, Figure 22—that is, that the strength of the current increases to a considerable height, but very slowly. Such a rate of change, even though the rise of intensity were continued until the strength of current was very great, would have no exciting effect upon a nerve and might fail to irritate a striated or non-striated muscle. A more rapid rise, such as is shown in *b*, might irritate a non-striated muscle, but fail to irritate a nerve or a striated muscle. With currents which rapidly gain their full intensity and then return again to zero, the following cases would be possible: A rapid rise and fall of intensity (see *c*), such as occurs by an induction shock or by the momentary closure of a battery current, might suffice to excite a nerve but not be an effective irritant to a striated, much less a non-striated muscle, unless the short duration of the current were compensated for by a considerable increase in the intensity (see *d*). On the other hand a form of variation such as is shown in *e*, where the rate of change is very rapid, although the intensity is not great, might act to irritate nerves, and, because of the longer duration of the current, striated muscles, though having no effect on non-striated muscles; and the slower rate of change, and considerable dura-

[1] *Beiträge zur vergleichende Physiologie der irritablen Substanzen*, Braunschweig, 1863.

tion, illustrated by *f*, though not affecting nerves, might suffice for striated muscles and be favorable to the excitation of non-striated muscles.

In the case of nerves, duration of current is less important than a rapid change of intensity. In the case of striated muscles the advantage to be gained by rapid variations can be easily overstepped, and the importance of the duration of the current is greater; while in the case of non-striated muscles duration of current is of the first importance and rapid variation may fail to excite. In the case of all tissues, strength and density of current, what we may call intensity of current, is favorable to excitation.

(*f*) *Effect of the Direction in which the Current flows along the Nerve.*— The result of the irritating change produced in a nerve by a battery current has been found to depend upon whether the current flows toward or away from the organ stimulated by the nerve. This fact can be most readily observed in the case of isolated motor nerves. In the case of these nerves, the effects produced by opening and closing the current are different according as the current is descending, *i. e.* flows through the nerve in the direction of the muscle, or ascending, *i. e.* flows through the nerve in the opposite direction. Moreover, by a given rate of change of intensity, the stimulating effect varies with the strength of the current employed. Pflüger in his celebrated monograph, *Untersuchungen über die Physiologie des Elektrotonus*, published in Berlin, 1859, p. 454, formulated the following rule for the result of excitations under varying conditions:

Pflüger's Law of Contraction.

	Ascending Current.		Descending Current.	
	Closing.	Opening.	Closing.	Opening.
Weak current	Contr.	Rest.	Contr.	Rest.
Medium "	Contr.	Contr.	Contr.	Contr.
Strong "	Rest.	Contr.	Contr.	Rest.

To understand this so-called "law of contraction" we must bear in mind certain fundamental facts, namely:

a. When a nerve is subjected to a battery current, an excitatory process is developed in the part of the nerve near the kathode when the current is closed, and in the part of the nerve near the anode when the current is opened (see p. 53).

b. The excitatory process developed at the kathode is stronger than that developed at the anode (see p. 53).

c. A third fact which is of no less importance, and which will be considered in detail when we study the effects of the constant current on the irritability and conductivity of nerve and muscle (see p. 95), is the following: During the time that a strong constant current is flowing through a nerve, the conducting power is somewhat lessened in the part to which the kathode is applied, and is greatly decreased, or altogether lost, in the region of the anode; moreover, at the instant that the current is withdrawn from the nerve the conducting power is suddenly restored in the region of the anode, and greatly lessened, or lost, in the region of the kathode.

The twelve cases included in the above table can be represented in the following diagram (Fig. 23), in which a cross is marked at the part of the nerve
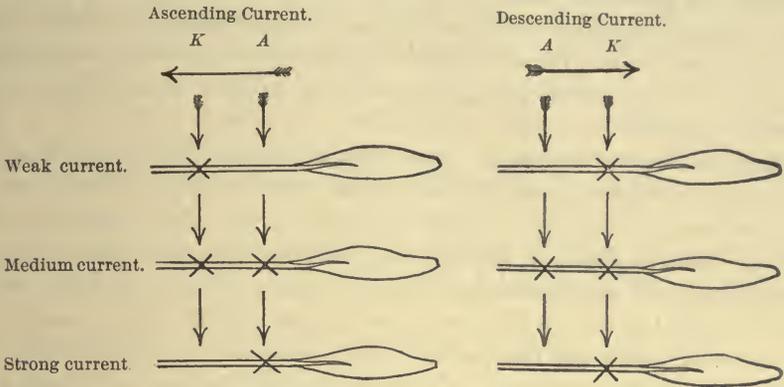

FIG. 23.—Diagram illustrating Pflüger's law.

from which the irritation which is effective in producing a contraction takes its rise.

In the case of fresh motor nerves of the frog, when the current is weak, only closing contractions, *i. e.* those originating at the kathode, are obtained by both directions of the current. As the strength of the current is increased, at the same time that the closing kathodic contractions grow stronger, opening anodic contractions begin to appear; and with currents of medium strength both closing and opening contractions are obtained with both directions of the current. If the strength of the current be still further increased, a change is observed; with a strong current, the closing of the ascending and the opening of the descending current fails to excite a muscular contraction. This fact is demonstrated most clearly if we employ two nerve-muscle preparations, and lay the nerves in opposite directions across the non-polarizable electrodes, so that the current from the battery shall flow through one of the nerves in an ascending direction and through the other in the descending direction (see Fig. 24). If under these conditions a strong battery current be employed, muscle *a* (through the nerve of which the current is descending) will contract only when the circuit is closed,

FIG. 24.—Effect of direction of current as shown by simultaneous excitation of two nerve-muscle preparations.

and muscle *b* (through the nerve of which the current is ascending) will contract only when the circuit is opened.

Since in the case of currents of medium strength, both opening and closing the circuit, when the current is ascending and when it is descending, develops a condition of excitation in the nerve sufficient to cause contractions, the failure of the contraction by the closing of the strong ascending current,

and by the opening of the strong descending current, can scarcely be supposed to be due to a failure of the exciting process to be developed in the nerve; and it would seem more likely that the nerve-impulse is for some reason prevented from reaching the muscle—which, as has been said, is the fact, the region of the anode being incapable of conducting during the flow of a strong current, and the region of the kathode losing its power to conduct at the instant such a current is opened.

Effect of Battery Currents upon Normal Human Nerves.—In experiments upon normal human nerves, the current cannot be applied directly to the nerve, but has to be applied to the skin over the nerve. As it passes from the anode, the positive electrode, through the skin, the threads of current spread through the fluids and tissues beneath, somewhat as the bristles of a brush spread out, and the current flows in a more or less diffuse stream toward the point of exit, where the threads of current concentrate again to enter the kathode, the negative electrode. This spread of the current is illustrated in Figure 25.

The density of the current entering any structure beneath the skin will depend in part upon the size of the electrode directly over it—that is, the amount to which the current is concentrated at its point of entrance or exit—in part on the nearness of the structure to the skin, and in part on the conductivity of the tissues of the organ in question as compared with the tissues and fluids about it. If the conditions be such as are given in Figure 25, the current will not, as in the case of the isolated nerve, enter the nerve at a given point, flow longitudinally through it, and then leave it at a given point; most of the threads of current will pass at varying angles diagonally through the part of the nerve beneath the positive

FIG. 25.—Rough schema of active threads of current by the ordinary application of electrodes to the skin over a nerve (ulnar nerve in the upper arm). The inactive threads are given in dotted lines (after Erb: *Ziemssen's Pathologie und Therapie*, Bd. iii. S. 76).

pole, then flow through the fluids and tissues about the nerve, until, at a point beneath the negative pole, the concentrating threads of current again pass through the nerve. A distinction is to be drawn between the physical and physiological anode and kathode. The physical anode is the extremity of the positive electrode, and the physical kathode is the extremity of the negative electrode; the physiological anode is the point at which the current enters the tissue under consideration, and the physiological kathode is the point where it leaves it. There is a physiological anode at every point where the current

enters the nerve, and a physiological kathode at every point where it leaves the nerve; therefore there is a physiological anode and kathode, or groups of anodes and kathodes, for the part of the nerve beneath the positive electrode, and another physiological anode and kathode, or collection of anodes and kathodes, for the part of the nerve beneath the negative electrode.

To understand the effect upon the normal human nerve of opening and closing the battery current, it is necessary to bear in mind three facts, viz.:

1. At the moment that a battery current is closed, an irritating process is developed at the physiological kathode, and when it is opened, at the physiological anode.

2. The irritating process developed at the kathode on the closing of the current is stronger than that developed at the anode on the opening of the current.

3. The effect of the current is greatest where its density is greatest.

The amount of the irritation process developed in a motor nerve is estimated from the amount of the contraction of the muscle. The contraction which results from closing the current, the closing contraction as it is called, represents the irritating change which occurs at the physiological kathode, while the contraction which results from opening the current, the opening contraction, represents the irritating change developed at the physiological anode. Since there are physiological anodes and kathodes under each of the two electrodes—the physical anode and physical kathode (see Fig. 26)—four possible cases may arise, namely:

1. *Anodic closing contraction*—i. e. the effect of the change developed at the physiological kathode, beneath the physical anode (the positive pole).

2. *Anodic opening contraction*—i. e. the effect of the change developed at the physiological anode, beneath the physical anode (the positive pole).
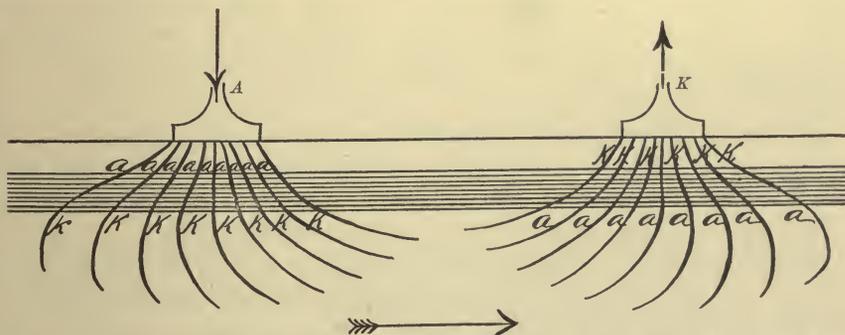
Fig. 26.—Diagram showing physical and physiological anodes and kathodes: *A*, the physical anode, or positive electrode; *K*, the physical kathode, or negative electrode; *a, a, a*, physiological anodes; *k, k, k*, physiological kathodes.

3. *Kathodic closing contraction*—i. e. the effect of the change developed at the physiological kathode, beneath the physical kathode (the negative pole).

4. *Kathodic opening contraction*—i. e. the effect of the change developed at the physiological anode, beneath the physical kathode (the negative pole).

For convenience these four cases are represented by the abbreviations ACC, AOC, KCC, and KOC.

These cases may be arranged in order according to the strength of the irritation which is developed.

Since the irritation process developed at a physiological kathode by closing a current, is, other things being equal, stronger than that developed at a physiological anode by opening the current, we should expect that the two closing contractions, KCC and ACC, would be stronger than the two opening contractions, KOC and AOC. This is the case, and as the current is more dense in the region of the physiological kathode, beneath the physical kathode, than at the physiological kathode, beneath the physical anode, KCC is stronger than ACC.

Of the two opening contractions, AOC is stronger than KOC because of the greater density of the current in the region of the physiological anode, beneath the physical anode, than in the region of the physiological anode, beneath the physical kathode.

These differences in the strength of the irritation process developed in these different regions is well shown by examining the reaction of nerves to currents of gradually increasing strength. The effect of the opening and closing irritation is seen to be as follows:

Weak currents.	Medium currents.	Strong currents.
KCC	KCC	KCC
———	ACC	ACC
———	AOC	AOC
———	———	KOC

The natural order, therefore, would be KCC, ACC, AOC, KOC. Sometimes, however, AOC is stronger than ACC; this happens when on account of the relation of the surrounding tissues to the nerve the density of the current at the physiological anode is great as compared with the density at the physiological kathode.

When the currents employed are strong, it not infrequently happens in the case of men that not only are the make and break followed by the usual rapid contractions of short duration, but during the closure of the current there is a continued contraction—galvanotonus, as it is sometimes called.

Conditions which Determine the Irritability of Nerves and Muscles. —We have thus far considered the conditions which determine the efficiency of such an irritant as the electric current. Other irritants are subject to like conditions, their activity being controlled to a considerable extent by the suddenness, strength, density, duration, and, possibly, direction of application. It is not necessary for us to consider how each special form of irritant is affected by these conditions; it will be more instructive for us to study how different irritants alter the irritability of nerve and muscle, and the relation of irritability to the state of excitation.

The power to irritate is intimately connected with the power to heighten

irritability—for a condition of heightened irritability is difficult to distinguish from a state of excitation. The irritability of cell-protoplasm is very dependent upon its physical and chemical constitution, and even slight alterations of this constitution, such as may be induced by various irritants, will modify the finely adjusted molecular structure upon which the normal response to irritants depends. If this change be in the direction of increased irritability, the result may be irritation. But we must defer the discussion of the relation of irritability to irritation until we have considered the conditions upon which the irritability of nerve and muscle depends. These conditions can be best studied in connection with the influences which modify them— namely :

(*a*) Irritants.

(*b*) Influences which favor the maintenance of the normal physiological condition.

(*c*) The effects of functional activity.

(*a*) *The Influence of Irritants upon the Irritability of Nerve and Muscle.— Effect of Mechanical Agencies.*—A sudden blow, pinch, twitch, or cut excites a nerve or muscle. All have experienced the effect of a mechanical stimulation of a sensory nerve, through accidental blows on the ulnar nerve where it passes over the elbow, "the crazy bone." The amount of mechanical energy required to cause a maximal excitation of an exposed motor nerve of a frog is estimated by Tigerstedt[1] to be 7000 to 8000 milligrammillimeters, which would correspond roughly to a weight of 0.500 gram falling fifteen millimeters—at least a hundred times less energy than that given out by the muscles in response to the nerve-impulse developed. Such stimuli can be repeated a great many times, if not given at too short intervals, without interfering with the activity of the nerve. A nerve can be irritated thirty to forty times, at intervals of three to four minutes, by blows from a weight of 0.485 gram, falling 1 to 20 millimeters, the contractions of the muscle, weighted with 30 to 50 grams, varying from minimal to from 3 to 4 millimeters in height. Rapidly following light blows or twitches applied to a motor nerve, by the tetanomotor of Heidenhain or Tigerstedt, excite a series of contractions in the corresponding muscles which fuse more or less into a form of continuous contraction, known as tetanus.

Mechanical applications to nerve and muscle first increase and later lessen and destroy the irritability. Thus pressure gradually applied first increases and later reduces the power to respond to irritants. Stretching a nerve acts in a similar way, for this also is a form of pressure ; as Valentin said, the stretching causes the outer sheath of the nerve to compress the myelin, and this in turn to compress the axis-cylinder. Tigerstedt states:[2] "From a tension of 0 up to 20 grams the irritability of the nerve is continually increased, but it lessens as soon as the weight is further increased."

Surgically the stretching of nerves is sometimes employed to destroy their

[1] "Studien über mechanische Nervenreizung," *Acta Societatis Scientiarum Fennicæ*, 1880, tom. xi. p. 32.　　　　　　　　　　　　　　　　　　　　[2] *Op. cit.*, p. 43.

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excitability. Slight stretching heightens the excitability and even quite vigorous stretching has only a temporary depressing effect unless it be carried to the point of doing positive injury to the axis-cylinder, and of causing degeneration. As nerves have the power to regenerate they may recover from even such an injury.

The irritability of muscles is likewise increased by moderate stretching and destroyed if it be excessive. Thus slight stretching produced by a weight causes a muscle to respond more vigorously to irritants. Similarly tension of the muscles of the leg, produced by slight over-flexion or extension, makes them more irritable to reflex stimuli, as in the case of the knee-jerk and ankle-clonus. Tension must be very marked to permanently alter the irritability of the muscles.

Effect of Temperature.—Changes in temperature, if sudden and extreme, irritate nerves and muscles. If the nerve or muscle be quickly frozen or plunged into a hot fluid it will be excited and the muscle be seen to contract. The cause of the irritation has been attributed to mechanical or chemical alterations produced by the change of temperature. The ulnar nerve at the elbow is excited if the part be dipped into ice-water and allowed to remain there until the cold has had time to penetrate; as is proved by the fact that in addition to the sensations from the skin, pain is felt which is attributed by the subject of the experiment to the region supplied by the nerve. As the effect of the cold becomes greater the pain is replaced by numbness, both the irritability and power of conduction of the nerve being reduced. Gradual cooling of motor nerves or muscles, and gradual heating, even to the point of death of the tissue, fails to excite contractions. It is stated that if a frog whose brain has been destroyed is placed in a bath the temperature of which is very gradually increased, the heating may be carried so far as to boil the frog without active movements having been called out. If a muscle be heated to 45° C. for frogs and 50° C. for mammals, it undergoes a chemical change, which is accompanied by a form of shortening different from the contraction induced by irritants. This form of contraction, though extensive, is feeble and is associated with a stiffening of the muscle, known as *rigor caloris*.

In general it may be said that raising the temperature above the usual temperature of the animal increases, while cooling decreases the irritability of the nerves and muscles. Cold, unless excessive and long continued, though it temporarily suspends does not destroy the irritability, while heat, if at all great, so alters the chemical constitution of the cell-protoplasm as to destroy its life.

The higher the temperature, the more rapid the chemical changes of the body and the less its power of resistance; low temperature, on the other hand, slows chemical processes and increases the endurance. It is noticeable that nerves and muscles remain irritable much longer than ordinarily in case the body be cooled before their removal. In the case of a mammal, the irritability may last from six to eight hours instead of two and a half, while in the case of frogs it may be preserved at 0° for ten days, although at summer heat it lasts only twenty-four hours. In the case of frogs which have been kept at a low

temperature the irritability becomes abnormally high when they are warmed to ordinary room-temperature.

Effect of Chemicals and Drugs.—The activity of nerve and muscle proto-plasm is markedly influenced by even slight changes in its constitution. If a nerve or muscle be allowed to lie in a liquid of a different constitution from its own fluid, and especially if such a liquid be injected into its blood-vessels, an interchange of materials takes place which results in an alteration of the constitution of the tissue, and a change in its irritability. Indeed, the only solutions which fail to alter the irritability are those which closely resemble serum and lymph. Fluids having other than the normal percentage of salts have a marked effect, while the absence of proteids appears to have little influence unless continued for a considerable time. These facts have been most clearly demonstrated in experiments upon the nature of fluids essential to the maintenance of the activity of isolated heart muscle. Most drugs and chemicals capable of influencing the irritability of nerves first increase and later destroy the irritability. It is said that sensory fibres are less susceptible to chemical stimulation than motor, but this is not certain. If the change in the chemical condition of the nerve or muscle be a rapid one, it is usually accompanied by the phenomenon of excitation ; if more gradual, the irritability alone is altered. The simple withdrawal of water from a motor nerve, by drying, or by strong solutions of neutral alkaline salts, urea, glycerin, etc., causes first an increase and later a decrease and loss of irritability. The increase of irritability is frequently accompanied by active irritation, the muscle in connection with the nerve showing rapid irregular contractions as different fibres of the nerve are one after the other affected. If the drying has not been too long continued, the irritability may be restored by supplying water. On the other hand, imbibition of distilled water may, by altering the relative amount of salts, or from mechanical causes, produce a lessening of irritability. If water be applied to the tissues by being injected into the blood-vessels, it first excites contractions and later causes a decline of irritability. Veratria, eserin, digitalis, alcohol, chloroform, ether, sublimate, mineral acids (except phosphoric), many organic acids, free alkalies, most salts of the heavy metals, destroy the irritability of nerves and muscles, as a rule after first producing increased excitability. Carbon dioxide, either because it is an acid or because of some specific effect, acid potassium phosphate, and lactic acid, lessen the irritability. Neutral potash salts, if concentrated, rapidly kill but excite less than do soda compounds. Many gases and fumes chemically irritate and kill nerve and muscle protoplasm.

Ammonia, neutral salts, carbon bisulphide, and ethereal oils may destroy the irritability of nerves without causing excitation, at least not sufficiently to produce visible contractions of the muscle. If directly applied, however, these substances excite muscles.

A sodium-chloride solution, of a strength of 6 parts per 1000 of distilled water, has been called the physiological solution because it was supposed to have no effect on the irritability of nerves and muscles ; but late experiments

have shown that even this if long continued first increases and later decreases the irritability of muscles. The cause of this is, however, probably the removal of other salts which are essential to the irritability, or the presence of carbonic acid.

From all these results it becomes evident that the normal irritability of nerves and muscles requires that a certain chemical constitution be maintained, and that even slight variations from this suffice to alter, and if continued to destroy, the irritability. Further, it is noticeable that in most cases the first step toward deterioration is a rise of irritability, which, if marked, is accompanied by a condition of irritation. If the cause of the increase in irritability and excitation be continued, sooner or later exhaustion supervenes, the irritability lessens, and finally is lost.

Effect of the Electric Current upon Muscles.—If a constant-battery current of medium strength be sent through a muscle for a short time, the muscle will give a single short contraction at the moment that the current enters it, and again when the current leaves it. If a strong current be used, the short closing contraction may be followed by a prolonged contraction (Wundt's closing tetanus), which, though gradually decreasing, may last as long as the current is closed; and when the current is broken, the usual opening contraction may be likewise followed by a prolonged contraction (Ritter's opening tetanus), which only gradually passes off. The closing contraction originates at, and the closing continued contraction may be limited to, the region of the kathode; and the opening contraction originates at, and the opening continued contraction may be limited to, the region of the anode.

In case a very weak current is used, no contraction will be observed; nevertheless, while the current is flowing through the muscle it modifies its condition; a state of latent excitation is produced at the kathode, which shows itself in an apparent increase of irritability of that part of the muscle. On the other hand, the irritability of the muscle at the kathode will be found to be lessened after the withdrawal of the polarizing current, because the condition of excitation which it causes fatigues that part of the muscle.

The effects of the battery current at the region of the anode are just opposite to those produced at the kathode. While the current is flowing, the irritability at the anode is lessened, and when the polarizing current is removed, irritability at the anode is found to be greater than it was before the battery current was applied.

The lessened irritability which is produced at the anode during the flow of the battery current may be shown by an inhibition of a condition of excitation which may be present at the time that the current is applied to the muscle. For example, in the case of unstriated muscles, not only does closing the battery circuit never cause a contraction at the anode, but if the part of the muscle exposed to the influence of the anode happens to be at the time in a condition of tonic contraction, the entrance of the current causes that part of the muscle to relax. The inhibitory influence exerted by the anode, as a result of the lowering of the irritability, is seen to a remarkable degree in its

effect upon the heart.[1] If the anode rest on the ventricle of the frog's heart, and the kathode at some indifferent point, relaxation is seen in the region of the anode with each systole of the ventricle. Inasmuch as the rest of the ventricle contracts, the pressure of the blood causes the wall of the ventricle to bulge out, and make a little vesicle at the region of the anode. A similar inhibitory influence may be observed upon an ordinary striated muscle at the point of application of the anode, if it be in a condition of tonic contraction when the battery current is sent into it. During the flow of the constant current through a muscle, the irritability is increased in the region of the kathode and decreased in the region of the anode. When the current is withdrawn from the muscle, on the other hand, the irritability of the kathode is found to be decreased, and at the anode to be increased.

Effect of the Electric Current upon Nerves.—The polarizing effects of a continuous constant current are the same upon a nerve as upon a muscle, with the exception that in the case of the nerve the condition of altered irritability is not so strictly limited to the point of application of the anode and kathode, but spreads thence throughout the part of the nerve between the two electrodes, the intrapolar region, as it is called, and for a considerable distance into the parts of the nerve through which the current does not flow, *i. e.* the extrapolar region. The term electrotonus has been applied to the effects of battery currents on nerves and muscles, and includes two sets of changes—(1) physiological, manifested by the alterations of irritability which we are considering ; (2) physical, exhibited in changes of the electrical condition of the tissue. The most important work on the influence of the constant current on the irritability of nerves was done by Pflüger. He ascertained the electrotonic effects of the polarizing current to be most vigorous in the immediate vicinity of the anode and kathode, and to spread thence in both directions along the nerve. He called the change produced in the nerve in the region of the anode " anelectrotonic," and the condition itself " anelectrotonus," while the change at the kathode was termed " katelectrotonic," and the condition " katelectrotonus." The same names are given to the effects of battery currents upon muscles.

To test the effect of a constant battery current upon the irritability of a nerve, put the nerve of a nerve-muscle preparation upon two non-polarizable electrodes (*A, K*, Fig. 27) which are placed at some little distance apart and at a considerable distance from the muscle. Connect these electrodes with a battery, introducing into the circuit a key (*k*), which permits the current to be quickly thrown into or removed from the nerve, and a commutator (*C*), which allows the current to be reversed and to be sent through the nerve in either the ascending or descending direction. Connect the muscle with a myograph lever, arranged so as to record the height of the muscle contractions. Then apply to the nerve at some point between the polarizing electrodes and the muscle a pair of electrodes (*I*) connected with the secondary coil of an induction apparatus, which is placed near enough to the primary coil to cause excitations of medium strength, and introduce into the secondary circuit a

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[1] Biedermann : *Elektrophysiologie,* 1895, p. 195.

short-circuiting key (*S*), by which the closing shocks can be prevented from reaching the nerve.

If, with this arrangement, a breaking induction shock of medium strength be given, the nerve will be excited, and the height of the muscular contraction which results may be taken as a test of the irritability of the nerve at *I*.
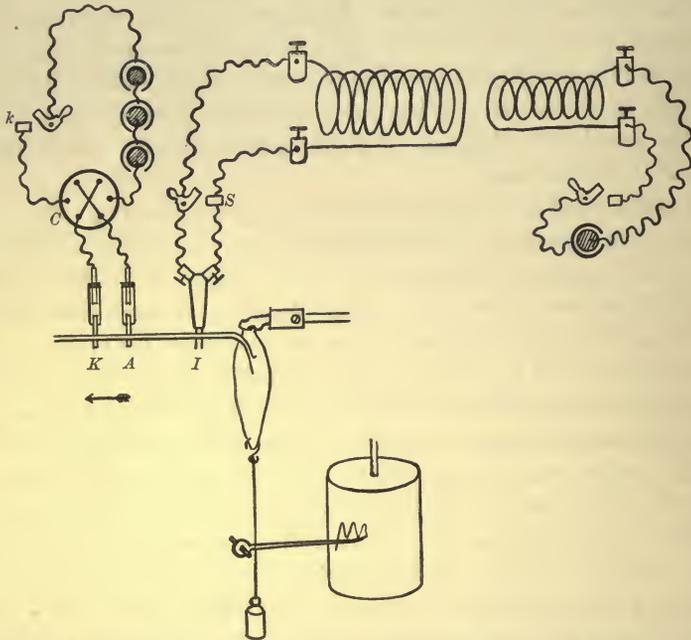

FIG. 27.—Method of testing anelectrotonic and katelectrotonic alterations of irritability in nerves.

Now send the polarizing current through the nerve, in the ascending direction, that is, with the anode nearer the muscle. At the moment the current is closed, if it be of medium strength, a closing contraction will be observed; then comes a period during which the muscle is not contracting and the polarizing current is apparently producing no effect on the nerve; if, however, after the current has acted a short time, the irritability of the nerve at the point *I* be again tested with a breaking induction shock, it will be found to be decreased, on account of the condition of anelectrotonus which has been induced. If the key in the polarizing current be then opened, the usual opening contraction will be recorded. After the polarizing current has been removed, the condition of the nerve at *I* can be again tested, and it will be seen that the irritability has returned to the normal, or is even greater than it was at the start.

The effect of the kathode on the irritability may be tested in a similar way, by reversing the polarizing current and again sending it into the nerve. This time the current will be descending, *i. e.* the kathode nearest the muscle. As before, a closing contraction will be seen when the circuit is made, but on testing the irritability at *I* with an induction shock of the same strength as before,

it will be found to be increased, the shock causing a larger contraction. On opening the polarizing current the usual opening contraction will be seen, and if after the current has been removed the irritability be again tested, it will be found to have returned to the normal, or to be decreased. The changes in irritability described can be ascertained by using mechanical or chemical stimuli as well as induction shocks. Alterations of the irritability induced by anelectrotonic and katelectrotonic changes of the nerve-substance are to be found not only in the part of the nerve between the point to which the polarizing current is applied and the muscle, but in the extrapolar region at the central end of the nerve, and in the intrapolar region. The experimental evidence of this is not so readily obtained, but there is no doubt of the fact.

The effect of the polarizing current is the greater, the better the condition of the nerve; moreover, the stronger the current employed, the more of the nerve influenced by it. Of course, in the intrapolar region there is a point where the effect of the anode to decrease the irritability comes into conflict with the effect of the kathode to increase it, and where, in consequence, the irritability remains unchanged. This indifferent point may be observed to approach the kathode as the strength of the current is increased. The following schema is given by Pflüger to illustrate the way in which the irritability is changed in the anelectrotonic and katelectrotonic regions as the strength of the current is increased :
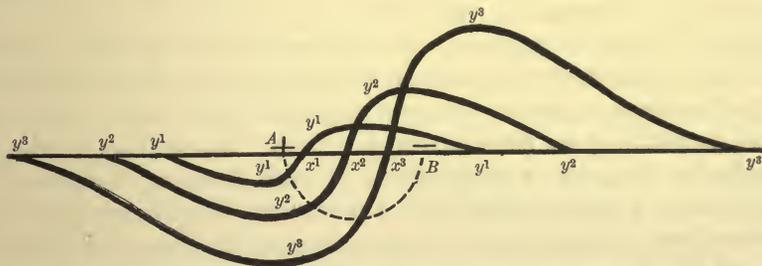
Fig. 28.—Electrotonic alterations of irritability caused by weak, medium, and strong battery currents: *A* and *B* indicate the points of application of the electrodes to the nerve, *A* being the anode, *B* the kathode. The horizontal line represents the nerve at normal irritability; the curved lines illustrate how the irritability is altered at different parts of the nerve with currents of different strengths. Curve y^1 shows the effect of a weak current, the part below the line indicating decreased, and that above the line increased irritability, at x^1 the curve crosses the line, this being the indifferent point at which the katelectrotonic effects are compensated for by anelectrotonic effects; y^2 gives the effect of a stronger current, and y^3, of a still stronger current. As the strength of the current is increased the effect becomes greater and extends farther into the extrapolar regions. In the intrapolar region the indifferent point is seen to advance with increasing strengths of current from the anode toward the kathode.

As in the case of the muscle, so of the nerve, the constant current leaves behind it important after-effects. In general it may be stated that wherever during the flow of the current the irritability is increased, there is a decrease of irritability immediately after the removal of the current, and *vice versa*. When the current is withdrawn from the nerve, the irritability in the region of the kathode is lowered, and in the region of the anode raised. It must be added, however, that the decrease of irritability seen at the kathode gradually passes over into a second increase of irritability, while the increase seen at the

anode upon the removal of the current continues a considerable time and is not reconverted to a decrease; therefore the total after-effect is an increase of irritability.

The fact that when the current is closed the irritation starts from the kathode, and when the current is opened from the anode, may well be associated with the changes in irritability which take place at the kathode and anode upon the closing and the opening of the current. The setting free of an irritation appears to be associated only with an increase of irritability. When the current is closed the establishment of the condition of katelectrotonus is accompanied by a rise of irritability at the kathode, and when the current is opened the cessation of the condition of anelectrotonus is likewise accompanied by a rise of irritability. In the first case the irritability rises from the normal to something above the normal, and in the second case the irritability rises from the condition of decreased irritability up to something above the normal irritability. The change from the normal to the anelectrotonic condition of decreased irritability, or from the katelectrotonic condition of increased irritability down to normal irritability, does not irritate. As has often been said, it is hard to distinguish between increase of irritability and irritation.

The effects produced by battery currents upon irritability are found to be associated with peculiar alterations in the electrical condition of nerves and muscles. The relation is a suggestive one, but cannot be taken as a definite explanation of the changes of irritability.

Effect of Frequency of Application of the Stimulus on Irritability.—We have seen that influences which act as irritants may also have an effect upon the irritability of the nerve or muscle. In order to produce this change they must be as a rule powerful, or act for a considerable time. Nevertheless, in the case of muscles, at least, even a weak irritant of short duration, if repeated frequently, tends to heighten irritability. For example, if a muscle be stimulated by separate weak induction shocks at long intervals, the effect of each shock is slight, and the change produced by it is compensated for by restorative processes which occur within the living protoplasm during the following interval of rest, and each of the succeeding irritations finds the mechanism in much the same condition; if, however, the shocks follow each other rapidly, each stimulation leaves an after-effect which may have an influence upon the effectiveness of the stimulus following it. As a result of this, induction shocks too feeble to excite contractions may, if frequently repeated, after a little time cause a visible movement, and shocks of medium strength, if given at short intervals, may each cause a larger contraction than its predecessor, until a certain height of contraction has been reached, beyond which there is no further increase possible. It is not known whether the irritability of nerves is similarly increased, nor is it known whether physiological stimuli exert such an influence. We shall consider these so-called " staircase contractions " more carefully later (see page 110). When irritations follow each other very rapidly, the whole character of the contraction is changed, and the muscle, instead of making rapid single contractions, enters into the condition of apparently continuous contrac-

tion known as tetanus, during which it shortens considerably more than it does when making single contractions. Increase in irritability plays only a comparatively small part in the production of this remarkable phenomenon, which we shall study more carefully when we come to the mechanical problems involved in muscular contractions.

Rapidly repeated stimuli, though at first favorable to activity of a muscle, soon exert an unfavorable influence by causing the lessened irritability which is associated with fatigue.

(b) *Influences which favor the Maintenance of the Normal Physiological Condition of Nerve and Muscle.—Effect of Blood-supply on Nerve and Muscle.* —The vascular system is a path of communication between the several organs and tissues, and the circulating blood is a medium of exchange. The blood carries nutritive materials from the digestive organs and oxygen from the lungs to all the tissues of the body, and it transports the waste materials which the cells give off to the excretory organs. In addition to these functions it has the power to neutralize the acids which are produced by the cells during action, and so maintain the alkalinity essential to the life of the cell; it supplies all parts with moisture; by virtue of the salts which it contains, it secures the imbibition relations which are necessary to the preservation of the normal chemical constitution of the cell-protoplasm; it distributes the heat, and so equalizes the temperature of the body; finally, in addition to these and other similar functions, it is itself the seat of important chemical changes, in which the living cells which it contains play an active part. It is not strange that such a fluid should exert a marked influence upon the irritability of the nerves and muscles. Since the metabolism of muscles is best understood, we will first consider the importance of the circulation to the muscle. Muscles, even in the so-called state of rest, are the seat of chemical changes by which energy is liberated, and when they are active these changes may be very extensive. If the cell is to continue its work, it must be at all times in receipt of materials to replenish the continually lessening store of energy-holding compounds; moreover, as the setting free of energy is largely a process of oxidation, a free supply of oxygen is likewise indispensable to action. These oxidation processes result in the formation of waste products—such as carbon dioxide, water, lactic acid—and these are injurious to the muscle protoplasm, and if allowed to accumulate would finally kill it. Of the services which the blood renders to the muscle there are, therefore, two of paramount importance, viz. the bringing of nutriment and oxygen and the removal of waste matter and surplus energy.

A classical experiment illustrating the effect of depriving tissues of blood is that of Stenson, which consists in the closure of the abdominal aorta of a warm-blooded animal by a ligature, or by compression. In the case of a rabbit, for example, the blood is shut off, not only from the limbs but from the lower part of the spinal cord. The effect is soon manifested in a complete paralysis of the lower extremities, sensation as well as power of voluntary and reflex movements being lost. The paralysis is due, in the first instance, to the

loss of function of the nerve-cells in the cord by which the muscles are normally excited to action. Later, however, the nerves and muscles of the limbs lose their irritability. Of the peripheral mechanisms the motor nerve-ends are found to succumb before the nerves and muscles. This is shown by the fact that although the muscles are still capable of responding to direct irritation, they are not affected by stimuli applied to the nerve, although the nerve at the time, to judge from electrical changes which occur when it is excited, is still irritable. Since the nerve and muscle are irritable, the lack of response must be attributed to the nerve-ends. The response to indirect stimulation (*i. e.* excitation of a muscle by irritating its nerve) is lost in about twenty minutes, while the irritability of the muscle, as tested by direct excitation, is not lost for four or five hours. In this as in so many instances the loss of irritability of the muscle is due primarily to the disturbance of the respiration of the muscle. Of the substances supplied to the muscle by the blood, oxygen is one the want of which is soonest felt. The muscle contains within itself a certain store of oxygen, but one which is by no means equal to the amount of oxidizable substances. Of this oxygen, that which is in the least stable combinations, and which is available for immediate needs, is soon exhausted. A continual supply of oxygen is required even for the chemical changes which occur in the quiet muscle. Of the waste substances which the blood removes from the cell, carbon dioxide is the one which accumulates most rapidly and is the first to lessen the irritability. Lactic acid and waste products from the breaking down of nitrogenous materials of the cell are also injurious.

The dependence of nerve-fibres upon the blood-supply is by no means so well understood. The nerve-fibre is a branch of a nerve-cell, and it seems as if the nourishment of the fibre was largely dependent upon that of the cell (see Fatigue of Nerve, p. 79). Nevertheless, the nerve-fibre requires a constant supply of blood for the maintenance of its irritability. The irritability of the nerve cannot long continue without oxygen, and a nerve which has been removed from the body is found to remain irritable longer in oxygen than in air, and in air than in an atmosphere containing no oxygen. Waste products liberated by active muscles have a deleterious effect on nerves; whether such substances are produced in the nerves themselves will be considered later.

The efficacy of the blood to preserve the irritability is to be seen in such experiments as those of Ludwig and Schmidt;[1] they succeeded in maintaining the artificial circulation of defibrinated, aërated blood through the muscles of a dog, and kept them irritable for many hours after death of the animal. If such an experiment is to be successful, the blood must be maintained at the normal temperature, be plentifully supplied with oxygen, and be kept as free from carbon dioxide as possible. Von Frey[2] made an elaborate experiment of

[1] *Sitzungsberichte der math.-phys. Classe der k. sächs. Gesellschaft der Wissenschaften*, vol. xx., 1868.
[2] "Versuche über den Stoffwechsel des Muskels," *Archiv für Anatomie und Physiologie*, 1885; physiologische Abtheilung, p. 533.

this nature. A dog was killed, the body was cut in halves, and the aorta and inferior vena cava were quickly connected with an apparatus for pumping the blood at a regular rate through the hind part of the body. Before the blood entered the arteries it passed through coils in which it was warmed to the normal temperature, and an artificial lung, where it received a supply of oxygen and was relieved of its carbon dioxide. Under these conditions the muscles were kept alive for more than seven hours, and so far retained their normal condition that throughout this period they were able to respond to stimuli sent to them through their nerves and contract with sufficient vigor to raise a considerable weight. H. N. Martin[1] made a similar experiment on the heart of a dog. The heart and lungs were isolated from the rest of the body, the heart was fed with defibrinated blood from a Mariotte's flask, and the lungs were supplied with air by an artificial respiration apparatus. The heart, which was kept moist and at the normal temperature, continued to beat for four hours and more.

Normally the blood-supply to the muscle is varied according to its needs. When the muscle is stimulated to action, its blood-vessels are at the same time dilated so that it receives a free supply of blood.[2] Moreover, if muscular work is extensive, the heart beats faster and the respiratory movements are quicker, so that a larger amount of oxygen is provided and the carbon dioxide is removed more rapidly. The importance of the blood-supply to a muscle can be best understood if we consider it in relation to the effects of fatiguing work upon the muscles. The relation of other substances in the blood to the needs of the muscle can be best considered together with the chemistry of the muscle.

Effect of Separation from the Central Nervous System.—If a motor nerve be cut, or if some part of it be so injured that the fibres lose their power of conduction, the portion of the nerve thus separated from the central nervous system sooner or later completely degenerates. Each of the motor nerve-fibres is a branch of a motor cell in the anterior horns of the spinal cord. These nerve-cells are supposed to govern the nutrition of their processes, though how a microscopic cell can thus influence a nerve-fibre a meter or so long is by no means clear. Soon after the nerve is separated from its cell it exhibits an increase of excitability near the point of section, and this change progresses down the fibre toward the periphery. The rule that the change in irritability progresses centrifugally along the motor nerves is known as the Ritter-Valli law. The increase is soon followed by a decrease of irritability. In the case of mammalian nerves loss of irritability may be complete at the end of three or four days, but the nerves of cold-blooded animals may retain their irritability for several weeks. The immediate cause of the loss of irritability is the change in the chemical and physiological structure of the axis-cylinder. The degenerative changes result finally in the complete destruction of the nerve-fibres, and involve the motor end-organs as well, but do not imme-

[1] *Studies from the Biological Laboratory of Johns Hopkins University*, 1882, vol. ii. p. 188.
[2] Sczelkow: *Sitzungsber. d. k. Akad. Wien*, 1862, vol. xlv. Abth. 1.

diately invade the muscle, which may be considered a proof that nerve and muscle protoplasm are not continuous.

Though no immediate change in the structure of the muscle is observable, the irritability of the muscle soon begins to alter. At the end of a fortnight the irritability of the muscle for all forms of stimuli is lessened. From this time on, the irritability gradually undergoes a remarkable change, the excitability for mechanical irritants and for direct battery currents beginning to increase, but the power to respond to electric currents of short duration, as induction shocks, continuing to lessen; indeed, the reactions of the muscle appear to take on more of the character of those of smooth muscle-fibres. The condition of increasing irritability to direct battery currents and mechanical irritants reaches its maximum by the end of the seventh week, and from that time on the power to respond to all forms of stimuli lessens, the excitability being wholly lost by the end of the seventh or eighth month. During the stage of increased excitability fibrillary contractions are often observed.

As in the case of a nerve so in the muscle the loss of irritability is due to degenerative changes which gradually lead to the destruction of the muscle protoplasm. The cause of the change in the muscle is still a matter of doubt, some regarding it as due to the absence of some nutritive, trophic influence from the central nervous system, while others consider it to be the result of circulatory disturbances, consequent upon the lack of a proper regulation of the blood-supply, due to the division of the vaso-motor nerves. As regards the latter view, it may be said that muscles whose vaso-motor nerves are intact, the vessels being innervated through other nerves than those which supply the muscle-tissue proper, as is the case with some of the facial muscles, undergo similar changes in irritability when their motor nerves are cut. As regards the former view, it may be said that if the muscles be artificially excited, as by electric stimuli, and thus are exercised daily, the coming on of degeneration can be at least greatly delayed. The question as to whether the anabolic processes within the muscle-cell are dependent on the central nervous system, in the sense of there being specific trophic influences sent from the nerve-cells to the muscles, is still under discussion and need not be considered further in this place. Without doubt the reflex tonus impulses which during waking hours are all the time coming to the muscles are productive of katabolic changes and, indirectly at least, favor anabolism.

(c) *Effect of Influences which result from the Functional Activity of Nerves and Muscles.*—*Fatigue of Muscles.*—The condition of muscular fatigue is characterized by lessened irritability, decrease in the rate and vigor with which the muscle contracts and liberates energy, and a still greater decrease in the rate with which it relaxes and recovers its normal form. In a sense, whatever induces such a state can be said to cause fatigue, but it is perhaps best to restrict the term to the form of fatigue which is produced by excessive functional activity. The cause of exhaustion which results from over-work is much the same as the cause of the loss of irritability and power

which follows the cutting off of the blood-supply. The working cell liberates energy at the expense of its store of nutriment and oxygen, and through oxidation processes forms waste products which are poisonous to its protoplasm. The fatigue which results from functional activity has, therefore, a twofold cause, the decrease in energy-holding compounds and the accumulation of poisonous waste matters.

It is evident that the length of time that the cell can continue to work will depend very much upon the rapidity with which the energy-holding explosive compounds are formed by the cell-protoplasm and the waste products are excreted. If a muscle is made to contract vigorously and continuously, as when a heavy weight is held up, fatigue comes quickly; on the other hand, a muscle may be contracted a great many times if each contraction is of short duration and considerable intervals of rest intervene between the succeeding contractions. The best illustration of this is the heart, which, though making contractions in the case of man at the rate of seventy or more times a minute, is able to beat without fatigue throughout the life of the individual. Each of the vigorous contractions, or systoles, is followed by an interval of rest, diastole, during which the cells have time to recuperate. The same is true of the skeletal muscles. It was found in an experiment that if a muscle of the hand, the *abductor indicis*, were contracted at regular intervals, a weight being so arranged that it was lifted by the finger each time the muscle shortened, a light weight could be raised at the rate of once a second for two hours and a half, *i. e.* more than 9000 times, without any evidence of fatigue. If, however, the weight was increased, which required a greater output of energy, or if the rate of contractions was increased, which shortened the time of repose, the muscle fatigued rapidly. In general, the greater the weight which the muscle has to lift, the shorter must be the periods of contraction in proportion to the interval of rest if the muscle is to maintain its power to work. Maggiora,[1] in his interesting experiments in Mosso's laboratory at Turin, made a very careful study of this subject, and ascertained that for a special group of muscles there is for each individual a definite weight and rate of contraction essential to the accomplishment of the greatest possible work in a given time. Either increasing the weight or the rate of contraction hastens the coming on of fatigue and so lessens the power and the total amount of work. In such an exercise as walking the muscles are not continually acting, but intervals of rest alternate with the periods of work, and the time for recuperation is sufficiently long to permit the protoplasm of the muscle-cells to prepare the chemical compounds from which the energy is liberated, as fast as they are used, and get rid of the waste products of contraction, so that vigorous muscles can be employed many hours before any marked fatigue is experienced. Sooner or later, however, the vigor of the muscle begins to decrease. The reason for this is not wholly clear. It is noticeable, however, that not only the muscles employed in the work, but other muscles, such as those of the arms for instance, even when purposely kept quiet, have their irritability

[1] *Archiv für Anatomie und Physiologie*, 1890; physiologische Abtheilung, p. 191.

reduced. This would suggest that the fatigue which finally asserts itself is due to some general rather than local influence. To understand this we must recall the fact that all parts of the body are in communication by means of the circulatory system. The ever-circulating blood as it is thrown out by the heart is divided into minute streams, which, after passing through the many organs of the body, unite again on their return to the heart. If materials be taken from the blood by one part, they are lost to all the rest, and if materials be added to the blood by any part, they are sooner or later carried to all the rest. During the course of a long march, the muscles of the leg take up a great deal of nutriment, and give off many waste products, and all the organs suffer in consequence. Mosso,[1] in his experiments upon soldiers taking long forced marches, found that lack of nutriment is not the only cause of the general fatigue produced by long-continued muscular work. The soldiers, though somewhat refreshed by the taking of food, did not recover completely until after a prolonged interval of rest. He attributed this to the fatigue-products which he supposed the muscles to have given off, and concluded that they were only gradually eliminated from the blood. To see if there were fatigue-products in the blood of a tired animal capable of lessening the irritability of organs other than those which had been working, he made the following experiment: He drew a certain weight of blood from the veins of a dog, and then put back into the animal an equal amount of blood from another completely rested dog. The dog which was the subject of the experiment appeared to be all right after the operation. On another day he repeated the experiment, but this time the blood which was put back was taken from a dog that was completely tired out by running. The effect of the blood from the fatigued animal was very marked; the dog receiving it showed all the signs of fatigue, and crept off into a corner to sleep. Mosso concluded from this experiment, that during muscular work fatigue-products are generated in the muscles, pass from thence into the blood, and are conveyed to other muscles, where they produce the lowered irritability and loss of power characteristic of fatigue. Many years before, Von Ranke extracted from the tired muscles of frogs substances which he considered fatigue materials. We know many of the waste products formed by muscles, and have learned that some of them lower the irritability, but what the exact substances are which produce the effects observed in the above experiments is not known.

Maggiora, in his experiments upon the fatigue of special groups of muscles, likewise found that the taking of food causes only a partial recovery of the tired muscles, and that an interval of rest is essential to complete recovery. In these experiments the irritability of the muscles was tested not only by volitional impulses, but by the strength of the electric current required to cause direct excitation. In the case of vigorous men, one and a half hours suffices to restore the muscles of the forearm which have been completely tired out by raising a heavy weight many times. He also observed that the time required for recovery can be greatly shortened if the circulation of the blood

[1] *Archiv für Anatomie und Physiologie*, 1890; physiologische Abtheilung.

and lymph in the muscles be increased by massage. This suggests that the power of the cell to give off its waste products to the blood is sufficiently rapid to keep pace with the ordinary production, but not with the more rapid formation taking place during fatiguing work. This would seem to be the case in spite of the fact that circulation of the blood in the muscles is increased during action. When muscles are stimulated to action by impulses coming to them from the central nervous system, the muscles in the walls of the blood-vessels of the muscle are also irritated by their vaso-dilator nerves, and, relaxing, permit a greater flow of blood through the muscle; when the muscles cease to be excited the muscles in the vessel walls are gradually contracted again through the action of the vaso-constrictor nerves, and the blood-supply to the muscle tissue is correspondingly lessened. This arrangement would seem to suffice for the bringing of nutriment and oxygen and the removal of waste matters under ordinary conditions.

Normally the muscles are never completely fatigued. It would seem that as the muscles tire and their irritability is lessened, the central nerve-cells which send the stimulating impulses to them have to work harder, and that the nerve-cells give out sooner than the muscles. On the other hand, certain experiments seem to show that the nerve-cells recover from fatigue more rapidly than the muscles do, so that it is an advantage to the organism that they should cease to excite the muscles before muscular fatigue is complete. With the decreasing irritability of the muscle, a feeling of discomfort in the muscle and an increasing sense of effort are experienced by the individual, both of which tend to cause a cessation of contraction, and prevent a harmful amount of work. That such an arrangement would be of service was apparent in the experiments of Maggiora, in which he found that if muscles are forced to work after fatigue has developed, the time of recovery is prolonged out of all proportion to the extra work accomplished.

Fatigue of Nerves.—Muscle-, gland- and nerve-cells—in fact, almost every form of protoplasm—if excited to vigorous long-continued action, deteriorate and exhibit a decline of functional activity. As we have seen, in the case of muscle there is a using up of energy-holding compounds and a production of poisonous waste matters, and these two effects induce the condition known as fatigue. *A priori*, we should expect similar changes to occur in the active nerve-fibre; almost all the experimental evidence is, however, opposed to this view. The form of activity which is most characteristic of muscle is contraction; that which is most characteristic of nerve is conduction. In the case of the muscle it is exceedingly difficult to distinguish between the effects produced by the processes associated with the change of form and those which result from the transmission of the excitatory change. There is little doubt but that fatigue is associated with the former; whether it is associated with the latter is not known. In the case of the nerve, where the transmission process may be studied by itself, conduction does not seem to fatigue (see p. 96).

Apparently the same may be said of the processes which result in the

development of what we call the nerve-impulse. We have already seen that the nerve may undergo an alteration of irritability if subjected to artificial irritants. Such a change at the point of application of the irritant is hardly to be regarded as a fatigue effect, however, for in many cases, at least, it is due to the direct effect of the irritant on the physical or chemical structure of the nerve-protoplasm rather than to molecular changes which are peculiar to the development of the nerve-impulse. Thus the change of irritability which results from a series of light blows, such as may be given to a nerve by Tigerstedt's tetanomotor, cannot properly be said to be the result of fatigue. It has been found that a medullary nerve may be excited many times a second for hours, by an induced current, and still be capable of developing at the stimulated point what we call the nerve-impulse. The change which is developed at the point of excitation and which passes thence the length of the nerve, would seem to be the expression of a form of energy liberated within the nerve, and since the liberation of energy implies the breaking down of chemical combinations, the apparent lack of fatigue of the nerve is incomprehensible. It is the more remarkable since the nerve-fibre is to be considered a branch of a nerve-cell, and nerve-cells appear to fatigue if frequently excited to vigorous action. Inasmuch as we have as yet no definite knowledge of the nature of what we call the nerve-impulse, or of the character of the processes by which it is transmitted along the nerve, we can afford to leave this question open, and simply state that the evidence thus far obtained is opposed to the view that nerve-fibres fatigue.

Effect of Use and Disuse.—Different kinds of muscle-tissues possess very different degrees of endurance. By endurance we mean the capacity to liberate energy during long periods of time. This capacity is intimately associated with irritability, for one of the first marks of failure of power is a decline of irritability. In general, the more irritable a muscle the less its endurance, because with an increase of irritability there is associated a more rapid and extensive liberation of energy in response to irritants. For example, the rapidly responding and acting pale striated muscles of the rabbit have less resisting power than the red striated muscles, while the sluggish unstriated muscle-fibres can contract a long time without suffering from fatigue.

The endurance of muscles of even the same kind may differ very considerably in the same individual, but the differences are more striking in the case of different individuals. One of the causes of this is the extent to which the muscles are employed. Use, exercise, is the most effective method of increasing not only the strength, but the endurance of the muscle. Though this fact is so well known as to scarcely need repeating, the explanation of it is by no means so clear. Undoubtedly one of the causes is a more perfect circulation in a muscle which is often used, but this is not all. It would seem as if the protoplasm of the muscle-cell was educated, so to speak, to be more expert in assimilating materials containing energy, in building up the explosive compounds employed in its work, and in excreting deleterious waste matters.

The effect of exercise upon irritability has not been thoroughly worked out.

It would seem as if there were a normal degree of irritability for each special form of muscle-tissue, and as if either an increase or decrease of the irritability above or below this level was a sign of deterioration. Exercise, if not excessive, is favorable to the maintenance of this normal physiological condition. Without doubt many of the differences which we attribute to the muscles of different men are really due to differences in the central nerve-cells, the action of muscles, rightly interpreted, being rather an expression of central nervous activity than the result of peculiarities of the muscles themselves. To exercise the muscles is to exercise the nerve-cells, and the effects of exercise upon these nervous mechanisms is of as much importance as the effect upon the muscles. In admiring visible proportions we must always bear in mind "the power behind the throne." "Beef" is of use to the athlete, but the muscles are merely the servants, and can accomplish nothing if the master is sick. The nerve-cells always give out before the muscles, and the man preparing for a contest should watch his nervous system more than his muscles. He who forgets this can easily over-train, and do himself a permanent injury, besides failing in the race.

Effect of Enforced Rest.—Not only is the strength of the muscles greatly increased by exercise, but a lack of exercise soon results in a loss of strength. This is seen when an individual is confined to his bed for even a comparatively short time, or when a limb is subjected to enforced rest by being placed in a splint. The cause is to be sought in changes peculiar to the muscle protoplasm itself, although reduced circulation may also play a part. The effect of prolonged rest on the irritability of muscles, is seen most markedly when they are separated from the central nervous system by injuries of their nerves (see p. 79). The lowered irritability which results from prolonged rest is not peculiar to muscles, but is shared by all forms of protoplasm.

C. CONDUCTIVITY.

Conductivity is that property of protoplasm by virtue of which a condition of activity aroused in one portion of the substance by the action of a stimulus of any kind may be transmitted to any other portion. For example, if the edge of the bell of a vorticella (see Fig. 2, p. 34) be irritated by a hair, not only do the movements of the cilia cease, but the contractile substance of the bell draws it into a more compact shape, and the fibrillæ of the stalk shorten and pull the bell away from the offending irritant. In such a case an exciting process must have been transmitted throughout the cell, and through several more or less differentiated forms of protoplasm. This property of conductivity is not known to be limited to any one peculiar structural arrangement of protoplasm distinguishable with the microscope, but is exhibited by a vast variety of forms of cell-protoplasm, and by plants as well as animals. The cytoplasm of cells, the part of the protoplasm surrounding the nucleus, appears to be composed of a semifluid granular material, traversed in all directions by finest fibrillæ which in some cases appear to form an irregular meshwork, the reticulum, and in others to be arranged side by side as more or less complete fibrils. It is not

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known whether the power of conduction is possessed by the whole of the protoplasmic substance or is confined to the reticular substance, but there are certain reasons why the former view may be considered the more probable.   The rate and the strength of the conduction process varies greatly in different forms of protoplasm, and there appear to be differences in the facility with which the exciting process spreads through different parts of even the same cell.[1] Not only are such differences to be noticed in many of the ciliated infusoria, but even the substance of striated muscles seems to conduct in two different ways, the sarcoplasm appearing to conduct slowly, and the more highly differentiated fibrillary portion of the fibre rapidly.   In general the process appears to be more rapid and vigorous where a fibrillated structure is observable.   Smooth muscle-tissue, which has a somewhat simple structure, conducts comparatively slowly; striated muscle, which is more highly differentiated, more rapidly, and the fibrillated axis-cylinder of the nerve-fibre, most rapidly of all.

Protoplasmic Continuity is Essential to Conduction.—*Effect of a Break in Protoplasmic Continuity.*—A break of protoplasmic continuity in any part of a nerve- or muscle-fibre acts as a barrier to conduction. If a nerve be cut through, the irritability and conductivity remain for a considerable time in the severed extremities, but communication between them is lost, and remains absent however well the cut extremities may be adjusted.   The nerve-impulse is not transmitted through the nerve-substance as electricity is transmitted along a wire : join the cut ends of a wire, and the contact suffices for the passage of the current ; join the cut ends of a nerve, and the nerve-impulse cannot pass. Any severe injury to a nerve alters the protoplasmic structure and prevents the chemical and physical processes through which conductivity is made possible.   It is probable that the same may be said of all forms of living cells, and the absence of protoplasmic continuity would seem to be an explanation of the fact that nerve- and muscle-fibres which lie close together may physiologically act as separate mechanisms.

Even in the case of apparently homogeneous protoplasm there is probably a definite structural relation of the finest particles, and upon this the physiological properties of the substance depends.   Slight physical and chemical alterations suffice to change the rate and strength of the conduction process, and the power to conduct is altogether lost if the protoplasm is so altered that it dies.

The relation of conductivity to structure of cell-protoplasm is illustrated in the effects of degeneration and regeneration upon the physiological properties of the nerve-fibre.   The life of the nerve-fibre is dependent on influences exerted upon it by the nerve-cell of which it is a branch.   When any part of the fibre is injured it loses its power to conduct, and the portion of the fibre separated by this block from its cell soon dies.   The irritability and conductivity are wholly lost at the end of three or four days, and the fibre begins to undergo degeneration.   The axis-cylinder and the myelin are seen to break up and are then absorbed, apparently with the assistance of the nuclei which normally lie just

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[1] Biedermann : *Elektrophysiologie*, 1895, p. 137.

inside the neurilemma, and which at this time proliferate greatly and come to occupy most of the lumen of the tube. The process of absorption is nearly complete at the end of a fortnight after the injury. Under suitable conditions, however, regeneration may occur, and as this takes place there is a recovery of physiological activities. The order in which conductivity and irritability return is instructive. Howell and Huber [1] made a careful study of this subject. They found that the many nuclei which develop during degeneration are apparently the source of new protoplasm, which is seen to accumulate in the old sheath until a continuous band of protoplasm is formed. About this thread of protoplasm a new membranous sheath develops, and thus is built up what closely resembles an embryonic nerve-fibre. The embryonic fibre formed in the peripheral end of the regenerating nerve joins that of the central end in the cicatricial tissue which has been deposited at the point of injury. Thus a temporary nerve-fibre is formed and united to the undegenerated part of the old fibre, and this new structure, though possessing neither myelin nor axis-cylinder, is found to be capable of conduction and to have a low form of irritability, being excitable to violent mechanical stimuli but not to induction currents. The power of conduction appears to return before irritability, and may be observed first at the end of the third week. Apparently sensation is recovered before the power of making voluntary movements; this difference may well be due, not to any essential difference between sensory and motor fibres, but to the fact that extra time is required for the motor fibres to make connection with the muscle. The embryonic fibre gradually gives place to the adult fibre, new myelin being formed all along the fibre, and a new axis-cylinder growing down from the old axis-cylinder. As the axis-cylinder grows down, the irritability for induction shocks is recovered. Many months may be necessary for the complete recovery of function.

The same is true of muscle as of nerve protoplasm,—the power of conduction ceases with the life of the cell-substance; thus, if the middle part of a muscle-fibre be killed, by pressure, heat, or some chemical, the dead protoplasm acts as a block to prevent the state of activity which may be excited at one end from being transmitted to the other, and the conduction power is only recovered on the regeneration of the injured tissue.

Isolated Conduction is the Rule.—(*a*) *Conduction in Nerve-trunks.*—The axis-cylinders of the many fibres which run side by side in a nerve-trunk are separated from each other by the neurilemma, and in the case of the medullary nerves by the myelin substance as well, so that there is not even contiguity, much less continuity of nerve-substance. Thus the many fibres of a nerve-trunk, some afferent and others efferent, though running side by side, conduct independently of one another. For example, if the skin of the foot be pricked, the excitation of its sense-organs is communicated to sensory nerve-fibres, and is transmitted along them to the spinal cord, where the stimulus awakens certain groups of cells to activity; these cells in turn, by means of their branches, the motor nerve-fibres, transmit the condition of excitation down to the mus-

[1] *Journal of Physiology*, 1892, vol. xiii. p. 361.

cle-fibres of the legs, which, when stimulated, contract and withdraw the foot from the offending irritant. The sensory and motor nerves concerned in this reflex act run for a considerable part of their course in the same nerve-trunk, but the sensory impulses have no direct effect on the motor nerve-fibres, and the roundabout course which has been described is the only way by which they can influence them.

It is probable that isolated conduction by separate fibres and their branches holds good within the central nervous system, as elsewhere, otherwise we could scarcely explain the localization of sensations, or co-ordinated movements. It is possible that within the central nervous system the neuroglia may act to secure isolated conduction. This question will be considered elsewhere.

(b) *Distribution of Excitation by Branches of Nerves.*—Nerve-fibres rarely branch in their passage along the peripheral nerves. The branches which are seen to be given off from the nerve-trunks are composed of bundles of nerve-fibres which have separated off from the rest, but which remain intact. After the nerves have entered a peripheral organ, or the central nervous system, the axis-cylinders may give off branches. Thus in muscles, and to a still greater degree in the electric organs of certain fish, the nerve-fibre and its axis-cylinder may divide again and again, or after entering the spinal cord the fibre may be seen to give off a great many lateral branches—collaterals, as they are called. It is not known whether in such cases the fibrillæ of the axis-cylinder give off branches, or whether they simply separate, a part of them entering the branch while the rest of them continue on in the main fibre. Though the exciting process does not pass from fibre to fibre, it probably involves in a greater or less degree all the elements of the same fibre, and passes into all its branches. It is evident that where it is necessary for the irritation to be localized, branching could not occur; but where a more general distribution is permissible, especially where several parts of an organ ought to act at the same instant, conduction through a single fibre which branches freely near its termination would be useful.

(c) *Conduction in Muscles.*—Each fibre of the muscles which move the bones—the skeletal muscles, as they are sometimes called—is physiologically independent of the rest. The sarcolemma prevents not only continuity, but contiguity of the muscle-substance of the separate fibres, and there is no cross conduction from fibre to fibre. Each of the separate muscle-fibres is supplied by at least one nerve-fibre, and, under normal conditions, only acts when stimulated by the nerve. In the case of plant-cells, and of certain forms of muscle-cells, about which there is a more or less definite wall or sheath, there are little bridges of protoplasm binding the cells together. For example, Engelmann describes the muscle of the intestines of the fly as composed of striated cells, sheathed by sarcolemma, except where bound together by little branches of sarcoplasma, which may act as conducting wires between the cells.

There are certain cells, however, which have been supposed to be exceptions to the rule that protoplasmic continuity is essential to conduction. The striated muscle-fibres of the heart are quite different from those of ordinary

skeletal muscles, physiologically as well as anatomically. They are stumpy, quadrangular cells, which are not known to have a sarcolemma, and which are united not only by their broad ends, but by lateral branches. Engelmann and others have considered conduction to take place in the heart from cell to cell, without the intervention of nerves, and in all directions with equal readiness. This view was held because the irritation was found to spread in all directions through the muscle-substance, and no nerves had been discovered which could account for this free communication. Quite lately, however, Hegmans and Demoor claim to have discovered in the heart of the frog, by the Golgi staining method, an anastomosing network of nerve-fibres which extends over the whole heart. This nervous network would appear to give ample means of communication between the different parts of the heart,[1] but it is possible that it has only a regulatory function.

The cells of the contractile substance of some of the medusæ (as Aurelia), have been supposed to communicate by contiguity rather than by continuity. The same has been thought to be the case with many forms of unstriated muscle-tissue;[2] moreover, there are groups of ciliated cells, the members of which act in unison although they have not been found to be connected either directly or by nerves. These cells have apparently no membranous covering, and though living as independent units, are so related that a condition of activity excited in one seems to be transmitted to the rest by means of contact, or through the mediation of cement-substance.

From what has been said it will be seen that protoplasmic continuity ensures free communication between different cells; that protoplasmic contiguity, either directly or through the mediation of the cement-substance, may possibly permit of conduction; but that the intervention of a different tissue, even as delicate as the sarcolemma, suffices to cause complete isolation of the cell from its neighbors.

Transmission of Excitation by means of End-organs.—The latest researches on the anatomy of the spinal cord seem to show that the incoming fibres do not communicate directly with nerve-cells, but terminate in brush-like endings in the immediate vicinity of the cells. A similar arrangement is found wherever nerve-cells are excited to action by nerve-fibres. It is doubtful whether the brush-like endings should be regarded as special exciting mechanisms, or whether the brush endings should be considered to be in contact with the nerve-cells or their protoplasmic processes, and this relation to be sufficiently close to permit the cells to be stimulated. The former view is favored by the fact that though the end-brush can excite the cell, the cell does not seem to be able to excite the brush. Much the same can be said of the end-plates by which the condition of excitation of nerve-fibres is conveyed to muscle-fibres, for they seem to be in contact with, rather than continuous with the muscle-substance. Though the nerve end-organ can excite the muscle, the muscle does not appear to be able to excite the nerve.

[1] *Archives de Biologie*, 1895, vol. xiii., No. 4, p. 619.
[2] Engelmann: *Pflüger's Archiv*, 1871, Bd. iv.

We have little knowledge of the physiological activities of the end-brushes. We know that much more time is lost in the central nervous processes than would be required to transmit the excitation through nerve-fibres, and that the time occupied is apparently the greater the longer the chain of nerve-cells entering into the act. A part of this time is undoubtedly spent in the processes occurring within the nerve-cells, but it is not unlikely that a portion of it may be spent by the nerve end-brushes in the excitation of the cells.

It is certain that the motor end-plates use up more time in the excitation of the muscles than would be required for the transmission of the irritation through a corresponding amount of nerve-substance. It is found by experiment that a muscle does not contract so quickly if it be excited through its nerve as when directly stimulated. Part of the lost time is spent in transmission of the excitation through the nerve, but after allowance has been made for this loss there is a balance to be accounted for, and this is credited to the motor end-plates. The average time used by the motor end-plate is found to be 0.0032 second.[1] There are many facts which go to show that the motor end-organ is different physiologically from the nerve; viz. the latent period of the motor end-plate, the effect of curare on the nerve end-plate as distinguished from nerve and muscle, the fact that the end-organ loses its vitality quicker than do nerve and muscle when the blood-supply is cut off, and the very existence of an end-organ distinguishable with the microscope.

Conduction in Both Directions.—(*a*) *In Muscle.*—Wherever protoplasmic continuity exists, conductivity would seem to be possible; moreover, the active change excited by an irritant would seem to be able to pass in all directions, though whether with the same facility is not known. Where the spread of the excitatory process is accompanied by a change in form, as is the case in many of the lower organisms and in muscle-tissue, it is not difficult to trace the process. The rate at which the excitation spreads through the irritable substance is very rapid, and special arrangements have to be employed to follow it, but the change is not so swift that its course cannot be accurately determined. It has been found that if a muscle-fibre be stimulated, as normally, by a nerve-fibre, the active condition produced at the point of stimulation spreads along the muscle-fibre in both directions to its extremities; if the fibre be artificially irritated at either end, the exciting change runs the length of the fibre, regardless of the direction, and stimulates every part of it to contraction.

(*b*) *In Nerves.*—In the cases of nerves where excitation is accompanied by no visible manifestation of activity, a definite answer to the question is not so readily obtained. As long as a nerve is within the normal body, the activity of the nerve-fibre can only be estimated from the response of the cell which the nerve-fibre excites, and there is such an organ only at one extremity of the fibre. Efforts have been made to elucidate the problem by attempting to unite the central part of a cut sensory nerve with the peripheral part of a divided motor nerve, and observing, after the healing was complete, whether excitation of the

[1] Bernstein: *Archiv für Anatomie und Physiologie*, 1882, p. 329.

sensory nerve caused movements in the part supplied by the motor nerve. With a similar purpose Paul Bert made a well-known experiment, in which he succeeded in bringing about union of the end of the tail of a rat with the tissues of the back, and found, when the union was complete, after the tail was cut off at its base, it was still capable of giving sensations of pain. All such experiments fail to throw light on the problem, for we now know that the peripheral part of the cut nerve dies, and the conduction power manifested later is dependent on new axis-cylinders which have grown down from the central nerve-stump.

There is, however, an entirely different method of experimentation which seems to prove that nerve-, like muscle-protoplasm, can conduct in both directions. This method is based on the fact that though nerve-fibres rarely branch in the peripheral nerve-trunks on their way to an organ, they may divide very freely after reaching it. Such branchings of fibres occur in muscle, and Kuehne[1] found that if one of these branches was stimulated, the irritation passed up the branch to the nerve-fibre and then down the other branches to the muscle. For example, he split the end of the sartorius muscle of a frog by a longitudinal cut, and then found on exciting one of the slips that the other contracted (see Fig. 29). Since cross conduction between striated muscle-fibres does not occur, no other explanation presents itself. Perhaps a still more striking example is to be found in an experiment of Babuchin[2] on the nerve of the electric organ of an electric fish, the Malopterurus. The organ, consisting of many thousand plates, is supplied by a single enormous nerve-fibre which after entering the organ divides very freely so as to supply every plate. In this case mechanical stimulation of the central end of one of the cut branches of the nerve sufficed to cause an electric discharge of the whole organ. The irritation must have passed backward along the irritated branch until the main trunk was reached and then in the usual direction down the other branches to the electric plates.

FIG. 29.—Kuehne's preparation of sartorius to show double conduction in nerve.

Still another method is that which was employed by Du Bois-Reymond,[3] on the fibres of the spinal nerve-roots. When a nerve is excited to action it undergoes a change in electrical condition, and this change progresses along the fibre at the same rate and in same direction as the nerve-impulse. This electrical change, though entirely different from the nerve-impulse itself, can be taken as an indication of the direction of movement of the process of conduction. Du Bois-Reymond found that if he stimulated the afferent fibres of the posterior spinal nerve-roots of the sciatic nerve of the frog, a "negative variation current," as the current resulting from the change in the electrical condition of the nerve is called, passed down the nerve in a direction

[1] *Archiv für Anatomie und Physiologie,* 1859, p. 595.
[2] *Ibid.,* 1877, p. 262.
[3] *Thierische Electricität,* 1849, Bd. ii. S. 587.

opposite to that which the normal impulse takes. Further, it was found that if the sciatic nerve was excited, a negative variation current could be detected in the anterior as well as the posterior roots. Normally the irritation only passes up the posterior roots and down the anterior, for normally the sensory fibres of the posterior roots are excited only at the peripheral end and the motor fibres of the anterior roots only at the central end. The experiment showed both sensory and motor fibres to be capable of conducting in both directions.

There is no doubt but that nerve-protoplasm can conduct in both directions, although normally the nerve is stimulated only at one end and therefore conducts in only one direction. This question is of considerable importance, not only with reference to the possibility of the central nervous system being influenced by stimuli passing from the muscles, for instance, back along the motor nerves, but more especially with reference to the spread of impulses through the central nervous system,—a problem which will be considered later with others of a similar character.

Rate of Conduction.—The activity of the conduction process varies greatly in different tissues. The nerves of warm-blooded animals conduct more rapidly than those of cold; in a given animal the nerve-fibres conduct more rapidly than muscle-fibres; striated muscle conducts more rapidly than smooth muscle; and even within a single cell different portions may transmit the exciting process at different rates; thus the myoid substance of the contractile fibres of one of the rhizopods conducts more rapidly than the less highly differentiated protoplasm of the cell. In general, it may be said that, " the power to conduct increases with increase of mobility and sensitiveness to external irritants, a fact which reveals itself in the protozoa, by a comparison of the slowly moving rhizopods with the lively flagellata and ciliata."[1] A study of different classes of muscle-tissue supports this view.

(a) *Rate of Conduction in Muscles.*—The conduction process is invisible, hence we estimate its strength and rate by its effects. It is most readily followed in such mechanisms as muscle, where the conducting medium itself undergoes a change of form as the exciting influence passes along it.

Rate of Transmission of Wave of Contraction.—If a muscle be excited to action by an irritant applied to one end, it does not contract at once as a whole, but the change of form starts at the point which is irritated and spreads thence the length of the fibres. At the same time that the muscle shortens it thickens, and under certain conditions the swelling of the muscle can be seen to travel from the end which is excited to the further extremity. In the case of normal, active, striated muscle, the rate at which the change of form spreads over the muscle is far too rapid to be followed by the eye, and hence the muscle appears to act as a whole. By suitable recording mechanisms, evidence can be obtained of the rate at which the exciting influence and contraction process pass along the fibre. Thus two levers can be so placed as to rest on the two extremities of a muscle, at the same time that the free ends of the levers

[1] Biedermann: *Elektrophysiologie,* 1895, Bd. i. S. 124.

touch a revolving cylinder, the surface of which is covered with paper blackened with lampblack. If, when the cylinder is revolving, one end of the muscle be stimulated, the record will show that the lever resting on that part is the first to move, making it evident that that part of the muscle begins to thicken first, and that the contraction does not begin at the further extremity of the muscle until somewhat later. The record given in Figure 30 was obtained in a similar experiment, but one in which the contraction of the muscle was registered by the

FIG. 30.—Rate of conduction of the contraction process along a muscle, as shown by the difference in the time of thickening of the two extremities. The tuning-fork waves record $\frac{1}{100}$ second (after Marey).

pince myographique and recording tambour of Marey (see Fig. 31).

Bernstein [1] measured the rate at which the irritating process is transmitted along the muscle by recording the latent period, the time elapsing between the
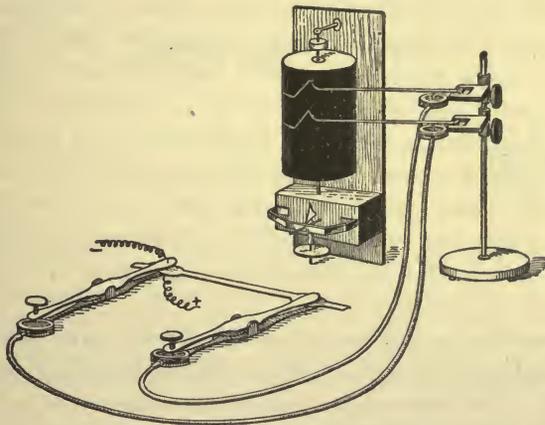
FIG. 31.—Method of recording the rate of passage of the contraction process along a muscle (after Marey). The movements of the muscle are recorded by means of air-transmission. The *pince myographique* consists of two light bars, the upper of which acts as a lever, moving freely on an axis supported by the lower. When the free end of the upper bar is raised, the other end presses down on a delicate rubber membrane which covers a little metal capsule, which is carried on the corresponding extremity of the lower bar. The capsule is in air-communication, by a stiff-walled rubber tube, with another capsule which is similarly covered with rubber membrane. A light lever is connected with the membrane of the second tambour, and records its movements on the surface of a revolving cylinder. The muscle is placed between the free ends of the bars of the *pince myographique*, and, when the muscle thickens in contraction, it raises one end of the lever, depresses the membrane at the other end, and drives air into the recording tambour, and thus, by automatically raising the writing-point, records its change in form on the cylinder.

moment of irritation and the beginning of the contraction (see p. 101). A lever was so connected with one end of the muscle as to record the instant that it began to thicken. The muscle was stimulated in one experiment at the end from which the record of its contraction was taken, and in another immediately

[1] *Untersuchungen über die elektrische Erregung von Muskeln und Nerven*, 1871, p. 79.

following experiment it was stimulated near the other end. The distance between the stimulated points being known, the rate of transmission was reckoned from the difference in the latent periods. In his experiments he found the rate of conduction in the semimembranosus of the frog to be from 3.2 to 4.4 meters per second. Hermann found the rate to be 2.7 meters for the curarized sartorius of the frog. The results obtained by Abey and some others are a little lower, but probably 3 meters per second can be accepted as the average normal rate for frog's muscle.

Length of Wave.—By such experiments it becomes obvious that the contraction process passes over the muscle, in the form of a wave. In an experiment, such as Bernstein's, in which the thickening of the muscle is recorded, we can determine from the length of the curve written by the contracting muscle how long the contraction remains at a given place. Knowing this, and the rate at which the process passes along the fibre, we can estimate the length of the contraction wave, just as we could reckon the length of a train of cars if we knew how fast it was moving and how long it required to pass a given station. Thus, if the contraction is found to last at a given point on the muscle 0.1 second, and the rate at which the contraction process is travelling is 3000 millimeters per second, the length of the wave is 300 millimeters. According to Bernstein's determinations, the length of the wave of contraction in a frog's striated muscle is from 198–380 millimeters. The length of a striated muscle-fibre is, at the most, scarcely more than 40 millimeters, and normally the muscle-fibre is stimulated, not as in the above experiment at one end, but near its centre, at the point where the nerve joins it; the irritation process spreads along the fibre in both directions from this point, and would pass over the distance 20 millimeters so quickly that practically the whole muscle-fibre would be in the same phase of contraction at the same time.

Rate of Conduction in Different Kinds of Muscle.—The rate of conduction varies very considerably in the muscles of different animals, and in different kinds of muscle in the same animal, just as the contraction process itself differs in its rate and strength.

	Meters per second.	
Smooth muscle-fibres of the ureters of the rabbit . . .	0.02–0.03	(Engelmann).
Muscle of the heart-ventricle of the frog	0.1	(Waller).
Contractile substance of medusæ	0.5	(Waller).
Neck-muscles of the turtle	0.1 –0.5	(Hermann and Abey).
Gracilis and semimembranosus of the frog . . . . ;	3.2 –4.4	(Bernstein).
Cruralis (red muscle) of the rabbit	3.4	(Rollet).
Sterno-mastoid of the dog	3. –6	(Bernstein and Steiner).
Semimembranosus (white muscle) of the rabbit . . .	5.4 –11.4	(Rollet).
Human muscle	10. –13	(Hermann).

(*b*) *Rate of Conduction in Nerves.*—Conductivity is most highly developed in the case of the nerve-fibre. The distances through which it acts and the rapidity of the process excite our wonder. The process is accompanied by no visible change in the nerve-fibre itself, and the strength and rate have to be

estimated by the effect produced on the organ which the nerve excites to action, or by the change which takes place in the electrical condition of the nerve as the wave of excitation sweeps over it.

Rate in Motor Nerves.—Helmholtz was the first to measure the rate of conduction in nerves.[1] Originally he employed Pouillet's method for measuring short intervals of time. The arrangement is illustrated in Figure 32. The moment that the current in the primary coil of an induction apparatus was broken and the nerve connected with the secondary coil received a shock, a current was thrown into the coils of a galvanometer (see p. 136). An instant after, the contraction of the muscle which resulted from the stimulation of the nerve broke the galvanometer circuit. The amount of deviation of the magnet of the galvanometer varied with the time that the circuit remained closed, and therefore could be taken as a measure of the interval elapsing between the stimulation of the nerve and the contraction of the muscle. The nerve was excited in two succeeding experiments at two points, at a known distance apart, and the difference in the time records obtained was the time required for the transmission of the nerve-impulse through this distance.
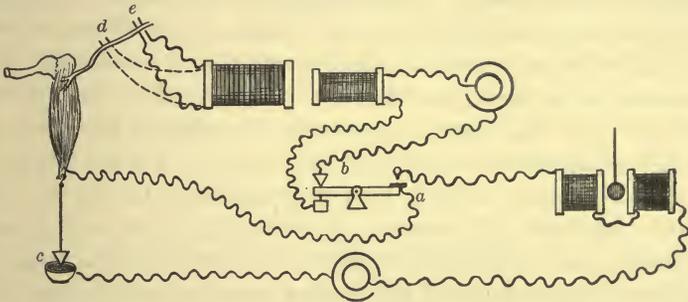
Fig. 32.—Method of estimating rate of conduction in motor nerve of frog, as used by Helmholtz. The horizontal bar *a–b* is supported on an axis in such a manner that when the contact is made at *a* it is broken at *b*, therefore at the same instant a current is made in the galvanometer circuit and opened in the primary circuit of the induction apparatus. When the muscle contracts, the galvanometer circuit is broken at *c*. The nerve was stimulated in two successive experiments at *d* and *e*.

Later, Helmholtz devised a method of directly recording the contractions of the muscle, and employed this to measure the rate of conduction in motor nerves. He stimulated the nerve as near as possible to the muscle and recorded the contraction, then he stimulated the nerve as far as possible from the muscle and again recorded the contraction. The difference in time between the moment of excitation and the beginning of the contraction in the two experiments was due to the difference in the distance that the nerve-impulse had to pass in the two cases, and, this distance being known, the rate of conduction could be readily calculated. By this means he found the rate of transmission in the motor nerves of the frog to be 27 meters per second. In similar experiments upon men he recorded the contractions of the muscles of the ball of the thumb, and noted the difference in the time of the beginning of the contractions when the median nerve was excited through the skin at two

[1] Helmholtz: *Archiv für Anatomie und Physiologie*, 1850, p. 71–276; 1852, p. 199.

different places. He found the average normal rate for man to be about 34 meters per second, a rate which is considerably quicker than that of our fastest express trains, but a million times less than the rate at which an electric current is transmitted along a wire. These determinations are still accepted as approximately correct for human nerves, although they are found to vary very considerably under different conditions, a high temperature and strong irritation quickening the rate to 90 or more meters per second. Moreover, considerable differences exist in nerves controlling different functions, even in the same animal. Thus Chauveau gives the rate for the fibres of the vagus nerve, which supply the rapidly contracting striated muscles of the larynx, as 66.7 meters per second; and the rate for vagus fibres, controlling the slower smooth muscles of the œsophagus, as 8.2 meters per second. The rate of transmission in the non-medullated nerves of invertebrates appears to be still slower; the nerve for the claw-muscles of the lobster conducts at a rate of from 6 to 12 meters per second, according as the temperature is high or low (Fredericq and Vandervelde).

Rate in Sensory Nerves.—We have no definite knowledge of the rate of conduction in sensory nerves. The attempt has been made to measure it, by stimulating the sensory fibres of a nerve-trunk at two different points and noting the difference in the time of the beginning of the resulting reflex acts; or, in experiments on men, the difference in the length of the reaction time has been taken as an indication. By reaction time is meant the interval which elapses between the moment that the irritant is applied and the signal which is made by the subject as soon as he feels the sensation. Oehl found the mean normal rate of conduction in the sensory nerves of men to be 36.6 meters per second.[1] Dolley and Cattell,[2] by employing the reaction-time method, found the rate for the sensory fibres of the median nerve of one of them to be 21.1 meters per second, and for the other 49.5 meters per second, while the posterior tibial nerve gave rates, for one of them 31.1 meters, and for the other 64.9 meters. They attribute these wide variations in part to differences in the effectiveness of the irritant at different parts of the skin, but chiefly to differences in the activity of the central nervous processes involved in the act.

In spite of the great difficulty of getting definite measurements on men, we may conclude from the work of these and other observers that the rate of conduction in sensory fibres is about the same as in motor fibres; in the case of man about 35 meters per second.

Influences which Alter the Rate and Strength of the Conduction Process.—(*a*) *Effect of Death-processes.*—Normally, the rate of conduction in muscle-fibres is so rapid that the whole muscle appears to contract at the same time; but there are certain conditions under which the transmission of the exciting influence is very much slowed, or even altogether prevented, so that the stimulation of a given part of the muscle results in a local swelling, or welt, limited to the excited area. When a muscle is dying, the rate of conduction as well

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[1] Oehl: *Archives italiennes de Biologie*, 1895, xxi., 3, p. 401.
[2] *Psychological Review*, New York and London, 1894, i. p. 159.

as the rapidity of contraction is lessened. The muscles of warm-blooded animals exhibit more striking differences than those of cold-blooded, but both are affected by them. If a dying muscle be mechanically stimulated, as by a direct blow, a localized swelling develops at the place; and if the muscle be stroked with a dull instrument, a wave of contraction may be seen to follow the instrument, the contraction being quite strictly limited to the excited area, so that one can write on the muscle. The strict localization of the contraction to the irritated parts makes it evident that the nerves take no part in it, hence Schiff called it an idio-muscular contraction, in distinction from the normal neuromuscular contraction. In the dying nerve as in the dying muscle the rate of transmission is found to be slowed.

(*b*) *Effect of Mechanical Conditions.*—The effect of pressure to lessen the conduction-power of nerves is one which everyone has had occasion to demonstrate on himself. For example, if pressure be brought to bear on the ulnar nerve where it crosses the elbow, the region supplied by the nerve becomes numb, "goes to sleep," so to speak. It is noticeable that only a slightly greater effort is required to move the muscles, at a time when no sensations are received from the hand. For some unexplained reason the sensory nerve-fibres appear to be less resistant than the motor. Gradually applied pressure may paralyze the nerve without exciting it, but on the removal of the pressure the recovery of function of the sensory fibres is accompanied by excitation processes, which are felt as pricking sensations referred to the region supplied by the nerve. The exact reason of the loss of functional power caused by pressure which is insufficient to produce permanent injury is not altogether clear. Stretching a nerve may act to lessen, and if severe destroy, conductivity. It is in one sense another way of applying pressure, since the calibre of the sheath is lessened and through the fluids pressure is brought to bear on the axis-cylinder. Of course, if the stretching were excessive, the nerve-fibres would be ruptured and degenerate.

(*c*) *Effect of Temperature on Conduction.*—Helmholtz and Baxt found that by cooling motor nerves they could lower the rate of conduction, and by heating them they could increase it even more markedly. By altering the temperature of the motor nerves of man, they observed rates varying from 30 to 90 meters per second. The rate of the motor nerves of other animals is likewise greatly altered by heat and cold. This is true of the invertebrates as well as the vertebrates; the rate in the nerves of the claw-muscles of the lobster, for example, changes from 6 to 12 meters per second as the temperature is varied from 10° to 20° C. Sensory nerve-fibres are similarly influenced by temperature. Oehl found by cooling and heating the nerves of men, variations of from 34 to 96 meters per second, and in some cases even greater differences were observed. Both the sympathetic and vagus nerve-fibres in the frog have their influence on the heart-beat decreased by cold and increased by heat.[1] The favorable influence of heat on the conduction power seems common to all nerves, but only within certain limits. The motor fibres of the sciatic of the frog lose their power to conduct at 41° to 44° C., but may recover the power

[1] Stewart: *Journal of Physiology*, 1891, vol. xii., No. 3, p. 22.

if quickly cooled; if the temperature has reached 50° C. conductivity is permanently lost.

Nerves of like function in different animals may lose the power of conduction at different temperatures. Thus the motor fibres of the sciatic nerve of the dog cease to conduct at 6° C., those of the cat at 5° to 3° C., of the frog at about 0° C. The inhibitory fibres of the vagus nerve of the dog show diminished activity at 3° C., and become wholly inactive at 0° C.; the inhibitory fibres of the vagus of the rabbit become inactive at 15° C.

Different kinds of fibres in the same nerve-trunk may be differently affected by temperature, and this difference may be sufficiently marked in some cases to be used as a means of distinguishing them.[1] For example, the temperature limits at which the vaso-constrictor fibres of the sciatic of the cat can conduct are 2°–3° C. to 47° C., while the limits for the dilator fibres are both lower and higher than for the constrictors. If cold be applied to the sciatic nerve, the fibres supplying the extensor muscles seem to fail before those which innervate the flexors.

Further, it has been observed that if cold be applied locally to a nerve, the part affected loses its power to conduct, and acts as a block to the passage of the nerve-impulse generated in another part of the nerve; on the other hand, the strength of an impulse is increased by passage through a region which has been warmed. These facts remind us of the effect of heat and cold on the activity of other forms of protoplasm and would find a comparatively easy explanation were we content to look upon conduction as the result of chemical change in the axis-cylinder. The fact that conduction does not cause fatigue is opposed to such an explanation, and so we take refuge in the idea that heat is favorable and cold unfavorable to molecular activity in general.

(d) *Effect of Chemicals and Drugs.*—The conductivity, like the irritability, of nerve and muscle is greatly influenced by anything which alters the chemical constitution of active substance. In general it may be said that influences which increase or decrease the one have a similar effect upon the other, but there are important exceptions to the rule. Thus the direct application of alcohol, ether, etc., may destroy the conductivity without greatly lessening the irritability, while carbon dioxide may destroy the irritability, though leaving the conductivity unimpaired.

(e) *Effect of a Constant Battery Current.*—A constant electric current, if allowed to flow through a nerve or muscle, not only alters the irritability but also the conductivity. The change in the conductivity affects both the strength and rate of the conduction process. Von Bezold[2] found that weak and medium currents have little effect on the conductivity, but that strong currents completely destroy the power of the nerve to transmit the nerve-impulse. As the strength of the current is increased the first effect is observed at the anode, and shows itself in a slowing of the passage of the exciting impulse. This action is the greater the more of the nerve exposed to the current, the stronger

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[1] Howell, Budgett, and Leonard: *Journal of Physiology,* vol. xvi., Nos. 3 and 4, 1894.

[2] *Untersuchungen über die elektrische Erregung den Nerven und Muskeln,* Leipzig, 1861.

the current, and the longer it is closed. The loss of conduction power is associated with changes at the place where the current enters and where it leaves the nerve rather than with alterations within the intrapolar region. Engelmann, in his experiments on the smooth muscle-fibres of the ureter, saw a decline of power of conduction at the anode by weak currents, which when the strength of the current was increased appeared also at the kathode; the conductivity was wholly lost at both poles when the current was very strong. In the case of a striated muscle, such as the sartorius of the frog, the kathode has been found to become impassable after strong currents have flowed through a muscle for a considerable time. The same is true of nerves.

It is not surprising that a current which can greatly decrease the irritability at the anode, and even inhibit a contraction which may be present when it is applied, should be found to decrease the conductivity as well, but that the conductivity should be decreased at the kathode, where the irritability is greatly increased, was not to be expected. Rutherford[1] found that with weak currents the rate of the conduction power at the kathode was increased rather than diminished, and that it was only when strong currents acted a considerable time that the conduction power lessened at the kathode. Biedermann explains this on the ground that the increased excitability at the kathode leads in the muscle to a condition of latent contraction and therefore to fatigue, and that it is this which lessens the conductivity. The lessened power to conduct continues at the kathode after the removal of the current. There is little doubt that fatigue interferes with the conduction power of muscle, but this explanation would hardly apply to nerves which are not known to fatigue at the point of stimulation, *i. e.* if we limit the term fatigue to changes resulting from physiological activity. Undoubtedly chemical and physical alterations may occur in nerves as a result of the passage of an electric current through them, and it would seem as if the loss of conductivity which they show when subjected to strong currents is to be accounted for by such changes.

The changes produced in the conductivity of nerves by strong currents explain the failure of the closing of the ascending current and opening of the descending current to irritate the muscle (see Pflüger's law, p. 60). In the former case the anode region of decreased conductivity intervenes between the kathode, where the closing stimulus is developed, and the muscle. In the latter case the irritation developed at the anode, on the opening of the current, is unable to pass the region of decreased conductivity which is formed at the kathode, and which persists after the current is opened.

Practical Application of Alterations produced by Battery Currents.—The alterations produced by strong battery currents in the irritability and conductivity of nerves and muscles may be made use of by the physician. If the effect of only one pole is desired, it may be applied as a small electrode immediately over the region to be influenced, while the other pole may be a large electrode placed over some distant part of the body where there are no important organs. The size of the electrodes used determines the density of the

[1] *Journal of Anatomy and Physiologie*, 1867, vol. 2, p. 87.

current leaving or entering the body and consequently the intensity of its action. The application of the anode to a region of increased excitability, by decreasing the irritability, may for the time lessen irritation; on the other hand the kathode may heighten the irritability of a region of decreased excitability. The sending of a strong polarizing current through a motor nerve, by lessening the conductivity, may prevent abnormal motor impulses from reaching muscles, and so stop harmful "cramps;" or the sending of such a current through a sensory nerve may, during the flow of the current, keep painful impulses from reaching the central nervous system. In applying a strong battery current to lessen irritability or conductivity it must be remembered that the after-effect of such a current is increased irritability.

(*f*) *Effect of Conduction.*—Many experiments have been made in the hope of detecting some form of chemical change as a result of conduction. The nerve has been stimulated for many hours in succession with an electric current, and then been examined with the utmost care to find whether there had been an accumulation of some waste product, as carbon dioxide, or some other acid body. The gray matter of the spinal cord, which is largely composed of nerve-cells, is found to become acid as a result of activity,[1] but this cannot be found to be the case with the white matter of the cord, which is chiefly made up of nerve-fibres, nor has an acid reaction been obtained with certainty in nerve-trunks.[2]

Not only has an attempt to discover this or other waste products which might be supposed to result from chemical changes within the nerve-fibre failed, but observers have been unable to obtain evidence of the liberation of heat, which one would expect to find were the nerve-fibre the seat of chemical changes during the process of conduction.[3] Stewart writes: "Speaking quite roughly, I think we may say that in the nerves of rabbits and dogs there is not even a rise of temperature of the general nerve-sheath of $\frac{1}{2000}$ of a degree during excitation."

Many experiments have been made to ascertain whether a nerve would fatigue if made to conduct for a long time. Most of these have been made upon motor nerves, the amount of contraction of the muscle, in response to a definite stimulus applied to the nerve, being taken as an index of the activity of the nerve. Since the muscle would fatigue if stimulated continuously for a long time, various means have been employed to block the nerve-impulse and prevent it from reaching the muscle, except at the beginning and end of the experiment. This block has been established by passing a continuous current through the nerve near the muscle, thus inducing an electrotonic

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[1] Funke: *Archiv für Anatomie und Physiologie*, 1859, p. 835. Ranke: *Centralblatt für medicinische Wissenschaft*, 1868 and 1869.

[2] Heidenhain: *Studien aus dem physiologischen Institut zu Breslau*, ix. p. 248; *Centralblatt für Medicin*, 1868, p. 833. Tigerstedt: "Studien über mechanische Nervenreizung," *Acta Societatis Scientiarum Fennicæ*, 1880, tom. xi.

[3] Helmholtz: *Archiv für Anatomie und Physiologie*, 1848, p. 158. Heidenhain: *op. cit.* Rolleston: *Journal of Physiology*, 1890, vol. xi. p. 208. Stewart: *ibid.*, 1891, vol. xii. p. 424.

change and non-conducting area;[1] or the nerve-ends were poisoned with curare (see p. 41), and the nerve excited until the effect of the drug wore off, and the nerve-impulse was able to reach the muscle;[2] or the part of the nerve near the muscle was temporarily deprived of its conducting power by an anæsthetic, such as ether. Another method of experimentation consisted in using the negative variation current of a nerve (see p. 140) as an indication of its activity, the presence of the current being observed with the galvanometer.[3] Other experimenters have examined the vagus nerve, to see if after long-continued stimulation it was still capable of inhibiting the heart, the effect of the stimulation being prevented from acting on the heart muscle during the experiment by atropin,[4] or by cold, applied locally to the nerve.[5] Still another method was to study the effect of long-continued stimulation on the secretory fibres of the chorda tympani, the exciting impulse being kept from the gland-cells by atropin.[6] Most of these experiments have yielded negative results, and it is doubtful whether nerves are fatigued by the process of conduction.

These results, of course, do not show that the nerve-fibres can live and function independently of chemical changes. As has been said, nerves lose their irritability in time if deprived of the normal blood-supply, and undoubtedly they are, like all protoplasmic structures, continually the seat of metabolic processes. The normal function of the nerve, however, the conduction of the nerve-impulse, seems to take place without any marked chemical change.

Nature of the Conduction Process.—There have been a great many views as to the nature of the conduction process, one after the other being advanced and combated as physiological facts bearing on the question have been accumulated. It has been suggested that the whole nerve moved like a bell-rope; that the nerve was a tube, and that a biting acid flowed along it; that the nerve contained an elastic fluid which was thrown into oscillations; that it conducted an electric current, like a wire; that it was composed of definitely arranged electro-motor molecules which exerted an electro-dynamic effect on each other; that it was made up of chemical particles, which like the particles of powder in a fuse, underwent an explosive change, each in turn exciting its neighbor; that the irritant caused a chemical change, which produced an alteration of the electrical condition of such a nature as to excite neighboring parts to chemical change and thereby to electrical change, and so alternating chemical and electrical changes progressed along the fibre in the form of a wave; finally, that the molecules of the nerve-substance underwent a form of physical vibration analogous to that assumed for light.

[1] Bernstein: *Pflüger's Archiv*, 1877, xv. p. 289. Wedenski: *Centralblatt für die medicinischen Wissenschaften*, 1884.

[2] Bowditch: *Journal of Physiology*, 1885, vi. p. 133.

[3] Wedenski: *loc. cit.* Maschek: *Sitzungsberichte der Wiener Academie*, 1887, Bd. xcv. Abthl. 3.

[4] Szana: *Archiv für Anatomie und Physiologie*, 1891, p. 315.

[5] Howell, Budgett, and Leonard: *Journal of Physiology*, 1894, xvi. p. 312.

[6] Lambert: *Comptes-rendus de la Société de Biologie*, 1894, p. 511.

A discussion of these different theories, none of which can be regarded as entirely satisfactory, cannot be entered upon here.

D. CONTRACTILITY.

Contractility is the property of protoplasm by virtue of which the cell is able to change its form when subjected to certain external influences called irritants, or when excited by certain changes occurring within itself. The change of form does not involve a change of size. The contraction is the result of a change in the position of the more fluid parts of the cell-protoplasm, and the effect is to cause the cell to approach a spherical shape. In the case of an amœba, for instance, excitation causes a drawing in of the pseudopods, and as the material in them flows back into the cell the body of the cell expands and acquires a globular form. In the simpler forms of contractile protoplasm the movement does not appear to be limited to any special direction, but in the case of the highly differentiated forms, such as muscle, both contraction and relaxation occur on definite lines.

When a muscle is excited to action, energy is liberated through chemical change of certain constituents of the muscle-substance, and this energy in some unknown way causes a rearrangement of the finest particles of the muscle-substance, and the consequent change of form peculiar to the contracted state. When the irritation ceases and relaxation takes place, there is a sudden return of the muscle-substance to the position of rest, either because of elastic recoil or of some other force at work within the muscle itself. That the recovery of the elongated form peculiar to the resting muscle is not dependent on external influences is evidenced by the fact that a muscle floating on mercury, and subjected to no extending force, will on the cessation of irritation assume its resting form. The relaxation no less than the contraction must be regarded as an active process, but on account of their flexibility muscle-fibres are incapable of exerting an expansion force, therefore cannot by relaxing do external work.

Both the histological structure and physiological action of the striated muscles which move the bones show them to be the most highly differentiated, the most perfect form of contractile tissue. It is by means of these structures that the higher animals perform all those voluntary movements by which they change their position with reference to external objects, acquire nourishment, protect themselves, and influence their surroundings. An exact knowledge of the method of action of these mechanisms and the influences which affect them is therefore of the greatest importance to us.

1. Simple Muscle-Contractions Studied by the Graphic Method.— When a muscle makes a single contraction, in response to an electric shock or other irritant, the change of form is too rapid to be followed by the eye. To acquire an adequate idea of the character of the movement it is necessary that we should obtain a continuous record of the alterations in shape which it undergoes. This can be done by connecting the muscle with a mechanism which enables it automatically to record its movements.

If one moves a pencil vertically up and down on a piece of paper, a straight line is written; if while the vertical movements are continued the paper be drawn along at a regular rate in a direction at right angles to the movement of the pencil, a curve will be traced. If the paper be moved at a regular rate, the shape of the curve will depend on the rate at which the pencil is moved, and, if the speed of the paper be known, the rate of movement of the pencil can be readily determined. This principle is employed in recording the movements of muscles. The muscle is connected with a mechanism which rises and falls as the muscle contracts and relaxes, and records the movement of the muscle on a surface which passes by the writing-point at a regular speed (see Fig. 35); such a record is called a myogram.

The Myograph.—The writing mechanism, together with the apparatus which moves the surface on which the record of the movement of a contracting muscle is taken is called a myograph. The writing mechanism has usually the form of a light, stiff lever, which moves very easily on a delicate axis; the lever is so connected with the muscle as to magnify its movements. The point of the lever rests very lightly against a glass plate, or surface covered with glazed paper, which is coated with a thin layer of soot. The point of the lever scratches off the soot, and the movements are recorded as a very fine white line. At the close of the experiment the record is made permanent by passing it through a thin alcoholic solution of shellac. The recording surface in some cases is in the form of a plate, in others of a cylinder, and is moved at a regular rate by a spring, pendulum, falling weight, clockwork, electric or other motor.[1]

The record which is traced with the myograph lever by the muscle has the form of a curve. From the height of the curve we can readily estimate the amount that the muscle changes its length, but in order to accurately determine the duration of the contraction process and the time relations of different parts of the curve, it is necessary to know the exact rate at which the recording surface is moving. The shape of the curve drawn by the muscle will depend very largely on the rate of the movement of the surface on which the record is taken. This is illustrated by the four records reproduced in Figure 33. These were all taken from the same muscle within a few minutes of each other and under exactly the same conditions, except that in the successive experiments the speed of the drum on which the record was traced was increased.

FIG. 33.—Records of four contractions of a gastrocnemius muscle of a frog: *a*, recording surface at rest; *b*, surface moving slowly; *c*, surface moving more rapidly; *d*, surface moving even faster.

A glance at these records shows that a knowledge of the rate of movement of the surface on which the record is taken is indispensable to an understanding of the time relations of the different parts of the

[1] See O. Langendorff; *Physiologische Graphik*, Franz Deuticke, Leipzig, 1891.

curve written by the muscle. The rate of movement of the recording surface can be registered by an instrument called a chronograph.

The chronograph (*g*, Fig. 34), consists of one or two coils of wire wound round cores of soft iron, and a little lever bearing a strip of iron, which is attracted to the soft-iron cores whenever they are magnetized by an electric current flowing through the coils of wire about them. When the current ceases to flow and the iron ceases to be magnetized, a spring draws the lever away from the iron. Many of the instruments employed for this purpose are
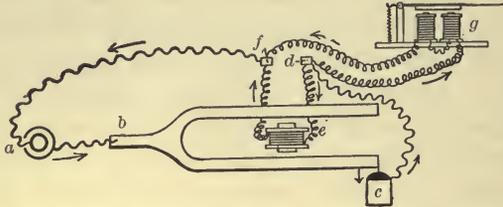
FIG. 34.—Method of interrupting an electric circuit by a tuning-fork, and of recording the interruptions by means of an electro-magnet: *a*, battery; *b*, tuning-fork, with platinum wire at the extremity of one of its arms, which with each vibration of the fork makes and breaks contact with the mercury in the cup below; *c*, mercury cup; *e*, electro-magnet which keeps the fork vibrating; *g*, chronograph. The current from the battery *a*, passes to the fork *b*, then, by way of the platinum wire, to the mercury in cup *c*, then to the binding-post *d*, where it divides, a part going through the coils of wire of the chronograph *g*, and thence to the binding-post *f*, the rest through the coil of wire of electro-magnet *e*, and then to the post *f*, from which the united threads of current flow back to the battery. The electro-magnet *e* keeps the fork in vibration, because when the platinum wire enters the mercury at *c*, the circuit is completed and the electro-magnet magnetizes its soft-iron core, which attracts the arms of the fork, and thus draws the wire out of the mercury and so breaks the circuit. When the current is broken the fork, being released, springs back, dips the wire into the mercury, and by closing the circuit causes the process to be repeated.

very delicate, and are capable of responding to very rapid interruptions of the current. The electric current is made and broken at regular intervals by a clock, tuning-fork (*b*, Fig. 34), or other interrupting mechanism, and the lever of the chronograph, which has a writing-point at its free end, moves correspondingly
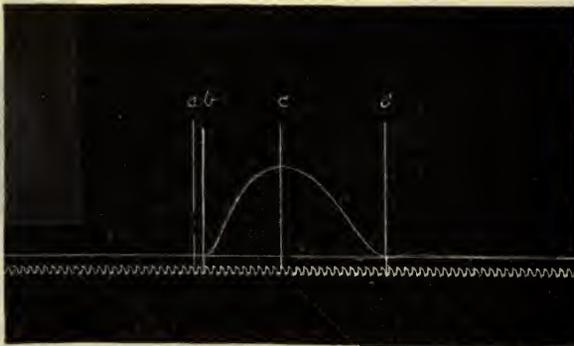
FIG. 35.—Myogram from gastrocnemius muscle of frog; beneath, the time is recorded in 0.005 second: *a*, moment of excitation; *b*, beginning of contraction; *c*, height of contraction; *d*, end of contraction.

and traces an interrupted line on the recording surface of the myograph (see Fig. 35). The space between the succeeding jogs marked by the chronograph lever is a measure of the amount of the surface which passed the point of the chronograph in one second, $\frac{1}{50}$ second, or $\frac{1}{100}$ second, as the case may be.

Myogram of Simple Muscle-contraction.—The rate of the movement of the muscle during every part of its contraction can be readily determined by comparing the record it has drawn with that of the chronograph.

Figure 35 is the reproduction of a single contraction of a gastrocnemius muscle of a frog. The rise of the curve shows that the contraction began comparatively slowly, soon became very rapid, but toward its close was again gradual; the relaxation began almost immediately, and took a similar course, though occupying a somewhat longer time. The electric current which actuated the chronograph was made and broken by a tuning-fork which made 200 complete vibrations per second, therefore the spaces between the succeeding peaks of the chronograph curve each represents 0.005 second. A comparison of the movements of the muscle with the tuning-fork curve reveals that about $\frac{5}{100}$ second elapsed between the point b, at which the muscle curve began to rise, and c, the point at which the full height of the contraction was reached, and that about $\frac{7}{100}$ second was occupied by the return of the muscle curve from c to point d, at the level from which it started. The muscle employed in this experiment was slightly fatigued, and the movements were in consequence a little slower than normal.

Latent Period.—The time that elapses between the moment that a stimulus reaches a muscle and the instant the muscle begins to change its form is called the latent period. In the experiment recorded in Fig. 35 the muscle received the shock at the point a on the curve, but the lever did not begin to rise until the point b was reached. The latent period as recorded in this experiment was about 0.006 second. The latent period and the time relations of the muscle-curve were first measured by Helmholtz, who introduced the use of the myograph.[1] Helmholtz concluded from his experiments that the latent period for a frog's muscle is about $\frac{1}{100}$ second, that the rise of the curve occupies about $\frac{4}{100}$, and the fall about $\frac{5}{100}$ second, the total time occupying about $\frac{1}{10}$ second. These rates can be considered approximately correct, excepting for the latent period, which has been found by more accurate methods to be considerably shorter. Tigerstedt connected a curarized frog's muscle with a myograph lever, which was so arranged as to break an electric contact at the instant that the muscle made the slightest movement; the break in the electric circuit was recorded on a rapidly revolving drum, by an electro-magnet similar to the chronograph. By this means he found the latent period of a frog's muscle may be as short as 0.004 second. Tigerstedt[2] did not regard this as the true latent period, however; he expressed the belief that the muscle protoplasm must have begun to respond to the excitation much sooner than this. The contraction of the whole muscle is the result of a shortening of each of the myriad of light and dark disks of which each of the muscle-fibres is composed (see Fig. 36). The distance to be traversed by the finest particles of muscle-substance is microscopic, hence the rapidity of the change of form of the whole muscle. Even such a change would require time, however, and it is probable

[1] *Archiv für Anatomie und Physiologie*, 1850, p. 308.
[2] *Ibid.*, 1885, Suppl. Bd., p. 111.

that the muscle protoplasm becomes active before any outward manifestation occurs. That this view is correct has been proved by electrical observations.

When muscle protoplasm passes from a state of rest to one of action it undergoes an alteration in electrical condition. This change can be detected by the galvanometer (Fig. 58, p. 135) or by the capillary electrometer (Fig. 59, p. 136). Burdon Sanderson[1] has found that by the aid of the latter instrument an alteration of the electrical condition of the muscle of a frog can be detected within 0.0025 second after the stimulus has been applied to it. Since some slight interval of time must have been lost even by this delicate method, it would seem that muscle protoplasm begins to be active at the instant it is stimulated.

According to this view, muscle-substance has no latent period; nevertheless we can still speak of the latent period of the muscle as a whole. It will be necessary, however, to distinguish between the electrical latent period and the mechanical latent period : by the former we mean the time which elapses between the moment of excitation and the first evidence obtainable of a change in the electrical condition of the muscle; by the latter, the time between excitation and the earliest evidence of movement which can be observed. In the case of the striated muscles of a frog the electrical latent period is about 0.0025 second, and the mechanical about 0.004 second. Mendelssohn[2] estimated the mechanical latent period of the muscles of man to be about 0.008 second. There can be little doubt, however, that this figure is too large.

Bernstein[3] found that if a normal frog's muscle be excited indirectly, by the stimulation of its nerve, the mechanical latent period is somewhat longer than when it is directly excited. Of course a certain length of time is required to transmit the excitation through the length of nerve intervening between the point stimulated and the muscle fibres. If this time be deducted, there still remains a balance of about 0.003 second, which can only be accounted for on the assumption that the motor nerve end-plates require time to excite the muscle-fibres. The motor end-plates are therefore said to have a latent period of 0.002–0.003 second.

The latent period, and the time required for the rise and fall of the myograph curve, are found to be very different not only for the muscles of different animals, but even for the different muscles of the same animal. Moreover, the time relations of the contraction process in each muscle are altered by a great variety of conditions.

Before considering the effect of various influences upon the character of the muscle contraction, let us give a glance at the finer structure of the muscle, and the change of form which the microscopic segments of the muscle-fibre undergo during contraction.

2. Optical Properties of Striated Muscle during Rest and Action.— An ordinary striated muscle is composed of a great number of very long

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[1] *Centralblatt für Physiologie,* July 5, 1890, vol. iv.

[2] *Archiv de Physiologie,* 1880, 2d series, vol. vii. p. 197.

[3] *Untersuchungen über den Erregungsvorgang im Nerven und Muskelsystem,* 1871.

muscle-cells, fibres as they are called, arranged side by side in bundles, the whole being bound together by a fine connective-tissue network. Each muscle-fibre consists of a very delicate elastic sheath, the sarcolemma, which is completely filled with the muscle-substance. Under the microscope the fibres are seen to be striped by alternating light and dark transverse bands, and on focusing, the difference in texture which this suggests is found to extend through the fibres, *i. e.* the light and dark bands correspond to little disks of substances of different degrees of translucency. More careful study with a high power, shows under certain circumstances other cross markings (see Fig. 36, *A*), the light band is found to be divided in halves by a fine dark line, *Z*, and parallel to it is another faint dark line, *n*, while the dark band, *Q*, is found to have a barely perceptible light line in its centre.

The fine dark lines, *Z*, which run through the middle of the light bands, were for a time supposed to be caused by delicate membranes (Krause's membrane), which were thought to stretch through the fibre and to divide it into a series of little compartments, each of which had exactly the same construction. Kuehne chanced to see a minute nematode worm moving along inside a muscle-fibre, and observed that it encountered no obstruction, such as a series of membranes, however delicate, would have caused. As it moved, the particles of muscle-substance closed in behind it, the original structure being completely recovered.

FIG. 36.—Schema of histological structure of muscle-fibre: *A*, resting fibre as seen by ordinary light; *B*, resting fibre seen by polarized light; *C*, contracting fibre by ordinary light; *D*, contracting fibre by polarized light.

This observation did away with the view that the fibre is divided into compartments, but the arrangement shown in Figure 36, *A*, repeats itself throughout the length of the fibre and indicates that it is made up of a vast succession of like parts.

Muscle-substance consists of two materials, which differ in their optical peculiarities and their reaction to stains. If a muscle-fibre be examined by polarized light, it is found that there is a substance in the dark bands which refracts the light doubly, is anisotropic, while the bulk of the substance in the light bands is singly refractive, isotropic (*B*, Fig. 36). The anisotropic substance is found to stain with hæmatoxylin, while the isotropic is not thus stained; on the other hand, the isotropic substance is often colored by chloride of gold, which is not the case with the anisotropic. By means of these reactions it has been possible to ascertain something as to the arrangement of these substances within the muscle-fibre, though the ultimate structure has not been definitely decided. It appears that the isotropic material is the sarcoplasma, which is distributed throughout the fibre and holds imbedded within it the

particles of the anisotropic substance, these particles having a definite arrangement. Striated muscle-fibres present not only cross markings, but under favorable conditions longitudinal striations, these being most evident in the dark bands. These longitudinal striations are looked upon with great interest as indicating that the particles of anisotropic material are arranged in long chains as incomplete fibrillæ. According to this view the muscle-fibre is composed of semifluid isotropic substance, in which are the particles of anisotropic material, arranged to form vast numbers of parallel fibrillæ of like structure, and so placed as to give the effect of transverse disks (Z, n, Q, Fig. 36).

When a striated muscle contracts, each of its fibres becomes shorter and thicker, and the same is true of the dark and light disks of which the fibres are composed. If we examine a muscle-fibre which has been fixed by osmic acid at a time when part of it was contracting, we see that in the contracted part the light and dark bands have both become shorter and wider, but that the volume of the dark bands (Q, Fig. 36, C) has increased at the expense of the light bands.

Further, the dark bands are seen to be lighter and the light bands darker in the contracted part, while examination with polarized light shows that though the anisotropic substance does not seem to have changed its position, (Fig. 36, D), the original dark bands have less and the lighter bands greater refractive power. These appearances would seem to be explained by Engelmann's view that contraction is the result of imbibition of the more fluid part of the sarcoplasm by the anisotropic substance; the cause of the imbibition is the liberation of heat by chemical changes which occur at the instant the muscle is excited. Engelmann[1] has shown that dead substance containing anisotropic material, such as a catgut string, can change its form, by imbibition of fluid under the influence of heat, and give a contraction curve in many respects similar to that to be obtained from muscle. This theory of the method of action of the muscle-substance, though attractive, can be accepted only as a working hypothesis, and is not to be regarded as proved. Various other theories have been advanced to explain the connection between the chemical changes which undoubtedly occur during contraction and the alteration of form, but none have been generally accepted. Enough has been said to show that the contraction of the muscle as a whole is the result of a change in the minute elements of the fibrillæ, and that the various conditions which influence the activity of the process of contraction must act chiefly through alterations produced in these little mechanisms.

3. **Elasticity of Muscle.**—The elasticity and extensibility of muscle are of great importance, for by every form of muscular work the muscle is subjected to a stretching force. Elasticity of muscle is the property by virtue of which it tends to preserve its normal form, and to resist any external force which would act to alter that form. The shape of muscles may be altered by pressure, but the change is one of form and not of bulk; since muscles are largely made up of fluid, their compressibility is inconsiderable. The elasticity

[1] *Ueber den Ursprung der Muskelkraft*, Leipzig, 1893.

of muscles is slight but quite perfect, by which is meant that a muscle yields readily to a stretching force, but on the removal of the force quickly recovers its normal form. Most of the experiments upon muscle elasticity have been made after the muscle had been removed from the body, hence under abnormal conditions. Under these circumstances it is found that if a number of equal weights be added to a suspended muscle, one after the other, the extension produced is not, like that of an inorganic body such as steel spring, proportional to the weight, but each weight stretches the muscle less than the preceding. If the weights be removed in succession, an elastic recovery is observed, which, although considerable, is incomplete. If the change in the length be recorded by a lever attached to the muscle, the surface being moved along just the same amount after each weight is added or removed, a curve is obtained such as is shown in Fig. 37, *b.* Above this is a record taken in a similar way from a piece of rubber (*a*). The rubber resembles a steel spring in that equal weights stretch it to like amounts, but the elastic recovery, though more complete than that of the muscle, is imperfect.

FIG. 37.—*a*, Curve of extensibility and elasticity of a rubber band; *b*, curve of extensibility and elasticity of a sartorius muscle of a frog. The weights employed were 10 grams each. The same length of time was allowed to pass between the adding and subtracting of the weights.

In such an experiment it is found that the full effect of adding the weights, or removing them from the muscle, does not occur immediately, but when a weight is added there is a gradual yielding to the stretching force, and, on the removal of a weight, a gradual recovery of form under the influence of the elasticity. This slow after-action makes it difficult to say just what is to be considered the proper curve of elasticity of muscle, especially as the physiological condition of the muscle is always changing. The elasticity of muscles is dependent on normal physiological conditions, and is altered by death, or by anything which causes a change in the normal constitution of the muscles, as the cutting off of the blood-supply. The dead muscle is less extensible and less elastic than the normal living muscle. Heating, within limits, increases, and cooling decreases the elasticity. Contraction is accompanied by increased extensibility, *i. e.* lessened elasticity, and the changes caused by fatigue lessen the elasticity. It is interesting to note in this connection that the elasticity is decreased by weak acid solutions and increased by weak alkaline solutions (Brunton and Cash).[1]

The elasticity of a muscle within the normal body is without doubt more perfect than that of an isolated muscle, and suffices to preserve the tension of the muscle under all ordinary conditions. The muscles are attached to the bones under elastic tension, as is shown by the separation of the ends in case

[1] *Philosophical Transactions*, 1884, p. 197.

a muscle be cut. This elastic tension is very favorable to the action of the muscle, as it takes up the slack and ensures that at the instant the muscle begins to shorten the effect of the change shall be quickly imparted to the bones which it is its function to move. The extensibility of the muscle is a great protection, lessening the danger of rupture of the muscle-fibres and ligaments, and the injury of joints when the muscles contract suddenly and vigorously, or when they are subjected to sudden strains by external forces. The importance of extensibility and elasticity to muscles which act as antag- onists is evident. When a muscle suddenly contracts against a resisting force such as the inertia of a heavy weight, the energy of contraction, which puts the muscle on the stretch, is temporarily stored in it as elastic force, and as the weight yields to the strain, is given out again; thus the effect of the contrac- tion force is tempered, the application of the suddenly developed energy being prolonged and softened.

4. **Influences which Affect the Activity and Character of the Con- traction.**—(*a*) *The Character of the Muscle.*—Attention has been called to the fact that irritability and conductivity may be different not only in different kinds of muscle-tissue, and in muscles of different animals, but even in similar kinds of muscle-tissue in the different muscles of the same animal; the same may be said of contractility. Although irritability, conductivity, and contrac- tility are to be regarded as different properties of muscle protoplasm, they are usually found to be developed to a corresponding degree in each muscle. Those forms of muscle which require for their excitation irritants of slow and prolonged action, are found to conduct slowly and to make slow and long- drawn-out contractions, and muscles which are excited by irritants acting rapidly and briefly are noted for the quickness with which they contract and relax.

Differences in the activity of the contraction process are made evident by the duration of single contractions of different forms of muscle-tissue. The duration of the contraction of the striated muscles of different animals differs greatly, *e. g.* of the frog $\frac{1}{10}$ second, of the turtle 1 second, of certain insects only $\frac{1}{300}$ second. Even muscles of apparently the same kind in the
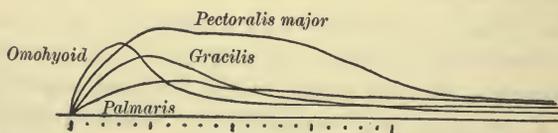
Fig. 38.—Records of maximal isotonic contractions of four different muscles from a turtle, each weighted with 30 grams: Pectoralis major; omohyoid; gracilis; palmaris. The dots mark ⅛ second, and the longer marks seconds (after Cash).[2]

same animal exhibit different degrees of activity. Cash[1] reports the following differences in the duration of the contractions of different striated muscles of a frog in fractions of a second: Hyoglossus, 0.205; rectus abdominis, 0.170; gastrocnemius, 0.120; semimembranosus, 0.108; triceps femoris, 0.104. Sim-

[1] *Archiv für Anatomie und Physiologie*, 1880, suppl. Bd., p. 147.   [2] *Op. cit.*, p. 157.

ilar differences are found to exist between different muscles in other animals —in the turtle, for instance, as is shown by the myograms in Fig. 38.

It is interesting to connect the rate of the contraction process in different muscles with their function. The omohyoid muscle of the turtle is capable of comparatively rapid contractions, and the action of this muscle is to draw back the head beneath the projecting shell; the pectoralis, on the other hand, although strong, contracts slowly; it is a muscle of locomotion and has to move the heavy body of the animal. Unstriated muscles, which are remarkable for the slowness and the duration of their contractions, are found chiefly in the walls of the intestines, blood-vessels, etc., which require to remain in a state of continued contraction for considerable periods and do not need to alter rapidly. It is the business of the heart-muscle to drive fluids often against considerable resistance, and a strong, not too rapid, slightly prolonged contraction, such as is peculiar to it, would be best adapted to its function. The bulk of the muscles of the bodies of warm-blooded animals are capable of rapid contraction and relaxation, but the rate normal to the muscle is found to vary with the form of work to be done. The muscles which control the vocal organs, for instance, have a very rapid rate of relaxation as well as of contraction. The muscles which move the bones appear to have different rates of contraction and relaxation according to the weight of the parts to be moved; those which control the lighter parts, as the hand, being capable of rapid contractions, while those which have to overcome the inertia of heavier parts, to which rapidity of action would be a positive disadvantage, react more slowly. In general, where rapid, brief, and vigorous contractions are required, pale striated muscles are found; where more prolonged contractions are needed, red striated muscles occur. The accompanying myograms (Fig. 39) illustrate
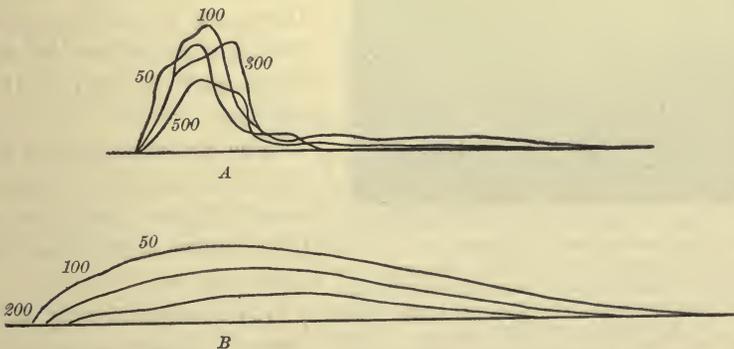
FIG. 39.—*A*, maximal contractions of the gastrocnemius medialis of the rabbit (pale muscle), weighted with 50, 100, 300, and 500 grams; *B*, maximal contractions of the soleus of the rabbit (red muscle), weighted with 50, 100, and 200 grams (after Cash).

the difference in the rate of contractions of pale and red striated muscles of the rabbit.

Pale and red striated fibres are found united in the same muscle in certain instances, and in these cases it is supposed that the former, which are capable

of very rapid and powerful but short-lived contractions start the movement, while the slower red muscles continue it.

(b) *Effect of Tension on the Extent and Course of the Contraction.*—As we have seen, the rate of the contraction of an ordinary striated muscle is much too rapid to be followed by the eye, and to study the course of the change in form it is necessary to employ some kind of recording mechanism. Every mechanical device for recording the movements of the muscle has inertia, and, if given motion, acquires momentum. Both of these factors would tend to alter the shape of the record, and the more, the greater the weight of the recording apparatus.

A weight, or tension, can be applied to a muscle in various ways, and the form of the contraction will be correspondingly changed. If a muscle is made to work with a considerable weight hanging on it, we speak of it as *loaded;* if the weight be connected with the muscle, but so supported that it does not pull on it until the muscle begins to shorten, the muscle is said to be *after-loaded;* if the weight is the same throughout the contraction, as when the muscle has only to lift a light weight, applied close to the axis of the lever, the contraction is said to be *isotonic;* if on the other hand the contracting muscle is made to work against a strong spring, so that it can shorten very little, *i. e.* has almost the same length throughout the contraction, the contraction is said to be *isometric.* The shape of the myogram recorded as a result of the same stimulus would evidently be very different in these four cases. The effect of a weight to alter the myogram is illustrated in the record given in Figure 40. Increasing the weight prolonged the latent period, and lessened the height and duration of the contractions.

Fig. 40.—Effect of the weight upon the form of the myogram. The gastrocnemius muscle of a frog excited by maximal breaking induction shocks five times, the weight being increased after each contraction, and in the intervals supported at the normal resting length of the muscle; *i. e.* the muscle was after-loaded: 1, muscle weighted only with very light lever; 2, weight five grams; 3, ten grams; 4, twenty-five grams; 5, fifty grams. The perpendicular line marks the moment of excitation. The time is recorded at the bottom of the curve by a chronograph, actuated by a tuning-fork vibrating 50 times per second.

The alterations liable to occur in the form of the myogram as a result of the mechanical conditions under which the work is done are—

(1) *Prolongation of the latent period.* There can be no movement of the lever until the inertia of the weight has been overcome, and the first effect of the contraction is to stretch the muscle, a part of the energy of contraction being changed to elastic force, which on the recoil assists in raising the weight.

(2) *Alteration in the shape of the ascending limb of the myograph curve.* The

weight will either lessen the rate at which the curve rises and decrease the height, or, if the weight be not great, it may acquire a velocity from the energy suddenly imparted to it by the muscle, which will carry the record higher than the absolute contraction of the muscle.

(3) *The fall of the curve may be altered.* The weight, suddenly freed by the rapidly relaxing muscle, may acquire a velocity in falling which will stretch the muscle-tissue, carry the record lower than the actual relaxation of the muscle would warrant, and lead to the development of artificial elastic after-oscillations.

These sources of error can be in part overcome by the employment of an exceedingly light, stiff writing-lever, and by bringing the necessary tension on the muscle by placing the extending weight very near the axis of the lever, so that it shall move but little and hence acquire little velocity.

(c) *Effect of Rate of Excitation on Height and Form of Muscular Contraction.*—If a muscle be excited a number of times by exactly the same irritant and under the same external conditions, the amount and course of each of the contractions should be exactly the same, provided the condition of the muscle itself remains the same. The condition of the muscle is, however, altered every time it is excited to contraction, and each contraction leaves behind it an after-effect. This altered condition is not permanent; as we have seen, increased katabolism is accompanied by increased anabolism, and, if the excitations do not follow each other too rapidly, the katabolic changes occurring in contraction are compensated for by anabolic changes during the succeeding interval of rest. Normally, a muscle, under the restorative influence of the blood, rapidly recovers from the alterations produced by the contraction process, and, therefore, if not excited too frequently, will give, other things being equal, the same response each time it is called into action. The best illustration of this is the heart, which continues to beat at a regular rate throughout the life of the individual. Tiegel found that one of the skeletal muscles of a frog, while in the normal body, can make more than a thousand contractions in response to artificial stimuli without showing fatigue; finally the effect of the work shows itself in a lessening of the power to contract. Every muscle contains a surplus of energy-holding compounds and also substances capable of neutralizing waste products, and even a muscle which has been separated from the rest of the body retains for a considerable time the ability to recover from the effects of excitation. It is evident that when a muscle is excited repeatedly, a certain interval of rest must be permitted between the succeeding excitations if its normal condition is to be maintained, and that the more extensive the chemical changes produced by the excitations the longer must be the periods allowed for recovery. This being the case, the rate of excitation and consequent length of the interval of rest will have a great effect upon the condition of the muscle and its capacity for work.

(1) *Effect of Frequent Excitations on the Height of Separate Muscular Contractions.*—Other things being equal, the height to which a muscle can contract when excited by a given irritant can be taken as an index of its capacity

to do work, and if a muscle be excited many times in succession, the effect of action upon the strength of the contraction process, the endurance, and the coming on of fatigue can be estimated from the height of the succeeding contractions. One might expect that every contraction would tend to fatigue and to lessen the power of the muscle, but almost the first effect of action is to increase the irritability and mobility of muscle protoplasm.

Introductory and Staircase Contractions.—The peculiar effect of action to increase muscular activity was first observed by Bowditch,[1] when studying the effect of excitations upon the heart. He found that repeated excitations of equal strength applied to the ventricle of a frog's heart caused a series of contractions each of which was greater than the preceding. If the contractions were recorded on a regularly moving surface, the summits of the successive contractions were seen to rise one above the other like a flight of steps. This peculiar phenomenon received the name of the " staircase contractions " (see Fig. 41).
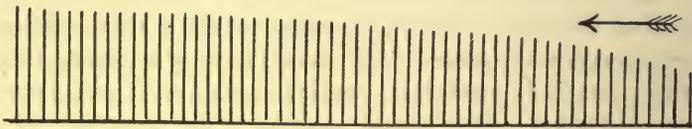
FIG. 41.—Staircase contractions of a frog's ventricle in response to a series of like stimuli, written on a regularly revolving drum by the float of a water manometer connected with the chamber of the ventricle (after Bowditch). The record is to be read from right to left.

This effect of repeated excitations was later observed by Tiegel,[2] on the skeletal muscles of frogs; by Rossbach,[3] on the muscles of warm-blooded animals, and by many others on various forms of contractile protoplasm.

The following series of contractions (Fig. 42), which closely resembles the above, was obtained from the gastrocnemius muscle of a frog, excited at a regular rate by a series of equal breaking induction shocks.
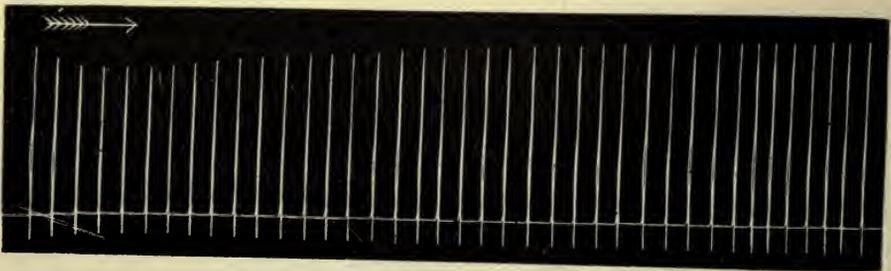
FIG. 42.—Staircase contractions of gastrocnemius muscle of a frog, excited once every two seconds by strong breaking induction shocks.

The contractions in Figure 42 did not begin to increase in height immediately; on the contrary, each of the first four contractions was slightly lower than the one which preceded it. A decline in the height of the first three or

[1] *Berichte der königlichen sächsischen Gesellschaft der Wissenschaft,* 1871.   [2] *Ibid.,* 1875.
[3] *Pflüger's Archiv,* 1882, 1884, Bd. xiii., xv.

four contractions is the rule when a normal resting muscle is called into action (see Figs. 43 and 46), and these contractions at the beginning of a series have received the name of the "introductory contractions." The introductory contractions appear to indicate that the first effect of action is to lessen irritability, or that anabolic changes are too slow to compensate for katabolic changes, and each of the first few contractions leaves behind it a fatigue effect. It is not long, however, before the influence of activity to heighten anabolism and increase irritability shows itself in the growth of the height of the succeeding contractions, and the "staircase contractions" are observed. This growth of the height of contractions must necessarily reach a limit, and the amount of increase is found to gradually lessen until the succeeding contractions have the same height. Sometimes the full height of the staircase is not reached before more than a hundred contractions have been made. These maximal contractions may be repeated many times; sooner or later, however, an antagonistic effect of the work manifests itself and the height of the contractions begins to lessen.

Effect of Fatigue.—A decline in the height of the contractions is an evidence of fatigue, and indicates that anabolism is failing to keep pace with
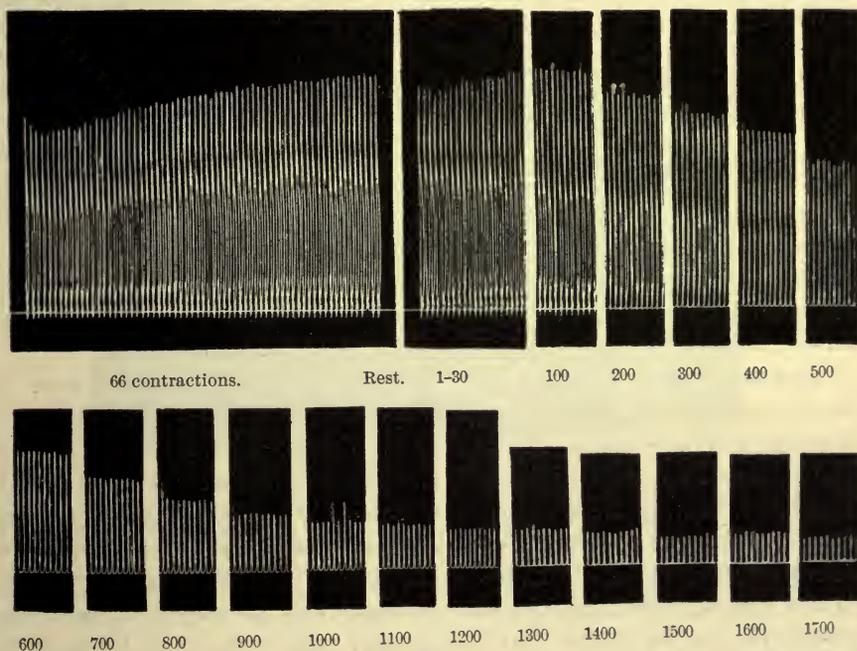
FIG. 43.—Effect of fatigue on the height of muscular contractions. The figure is a reproduction of parts of a record of over 1700 contractions made by an isolated gastrocnemius muscle of a frog. The contractions were isotonic, the weight being about 20 grams. The stimuli were maximal breaking induction shocks, and were applied directly to the muscle, at the rate of 25 per minute. Between the first group of 66 contractions and the following groups a rest of five minutes was given; after this rest the work was continued without interruption for about one and a half hours. The second group of contractions, that immediately following the period of rest, contains the first twenty contractions of the new series; the next group the 100th to the 110th; the next the 200th to the 210th, and so on.

katabolism. From this time on, the height of the succeeding contractions continually lessens, and often with great regularity, so that a line drawn so as to

connect the summits of the declining contractions, the "curve of fatigue," as it is called, may be a straight line. In the experiment, parts of the record of which are reproduced in Figure 43, an isolated gastrocnemius muscle of a frog was excited with maximal breaking induction shocks at the rate of 25 times a minute for about one and one-half hours; the contractions were isotonic, and the total weight of lever and load did not exceed 20 grams; the records of the succeeding contractions were recorded on a slowly moving cylinder. The experiment consisted of two parts—in the first 66 contractions, in the second over 1700 contractions were made; an interval of rest of five minutes was permitted between the two series.

In the first part of the experiment there was a decline in the height of the contractions for the first five contractions, the "introductory contractions," then during the next sixty-one contractions a gradual rise in the height of the contractions, the "staircase contractions." These phenomena repeat themselves in the second part of the experiment, that following the interval of rest. The contractions at the beginning of the second series were not so high as those at the end of the first series, though somewhat higher than those seen at the beginning of the first series; the rest of five minutes was not sufficient to entirely do away with the stimulating influence of the preceding work. The contractions of the second series took the following course: The first four introductory contractions gradually declined, then came the staircase contractions, which continued to rise until the 100th contraction, when a gradual lessening of the height of the contractions began. This decline continued throughout the long series of more than 1700 contractions given in the record, and, had the experiment been continued, would have undoubtedly gone on until the power was completely lost. The curve of fatigue was not a straight line, but fell somewhat more rapidly during the early part of the work than toward the end.

That the peculiar changes in the height of the contractions which occur in the early part of an experiment such as that which we have described are not abnormal, and the result of the artificial conditions under which the work is done, is shown not only by the fact that they are observed when a muscle which has its normal blood-supply is rhythmically excited to a large number of contractions, but by the personal experience of every one accustomed to violent muscular exercise. Everyone is conscious that he cannot put out the greatest muscular effort until he has "warmed up to the work." The runner precedes the race by a short run; the oarsman takes a short pull before going to the line; in all the sports one sees the contestants making movements to "limber up" before they enter upon the work of the game. These preliminary movements are performed not only to put the muscles in better condition for action, but to ensure more accurate co-ordination—that is to say, the facts ascertained for the muscle can be carried over to the central nervous system. The finely adjusted activities of the nerve-cells which control the muscles reach their perfection only after repeated action.

In such experiments as that recorded in Figure 43 the record shows to

a remarkable degree the fact that at any given time the muscle has a definite capacity for work. A suitable explanation of this is lacking. The correspondence in the height of the contractions of the same group, and the difference in the height of different groups of contractions, must be attributed to the existence within the muscle-cell of some automatic mechanism which regulates the liberation of energy and which has its activity greatly influenced by the alterations which result from action. Whether this supposed automatic regulatory mechanism controls both the preparation of the final material from which the energy displayed by the muscle is liberated, and the amount of the explosive change which results from the application of the irritant, cannot be definitely said.

(2) *Effect of Frequent Excitations upon the Form of Separate Contractions.* —The effect of activity is not only observable in the change in the height of the muscular contractions, but in the length of the latent period, in the rate at which the muscle shortens, and, above all, in the rate at which the muscle relaxes. The effect of a large number of separate contractions, made in quick succession, upon the rate at which the muscle changes its form during contraction, is illustrated in the myograms reproduced in Figure 44.
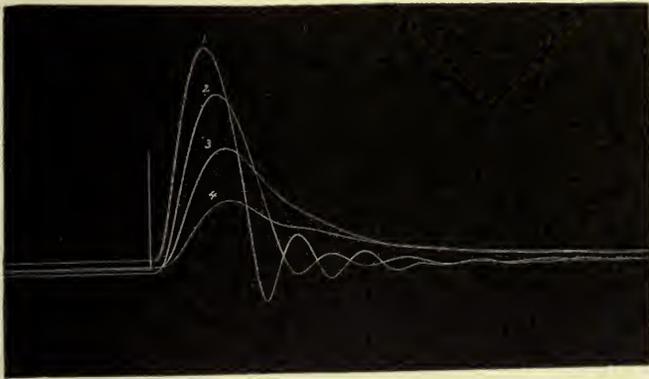
Fig. 44.—Effect of excitation upon the form of separate contractions. In this experiment the records of the muscular contractions were taken upon a rapidly revolving drum. The muscle was the gastrocnemius of the frog; the contractions were isotonic; the weight was very light, about 10 grams; the stimuli were maximal breaking induction shocks; and the rate of stimulation was twenty-three per minute. 1 marks the first contraction; 2, the 100th; 3, the 200th; 4, the 300th. The muscle was excited automatically by an arrangement carried by the drum, and the excitation was always given when a definite part of the surface of the drum was opposite the point of the lever which recorded the contractions.

In Figure 44 only the 1st, 100th, 200th, and 300th contractions were recorded. The perpendicular line marks the point at which the stimulus was given. In this experiment the latent period for each of the succeeding contractions is seen to be longer; the height is lessened; the rise of the curve of contraction is slowed and the curve of relaxation is even more prolonged. These and certain other changes are to be observed in the records of Figure 45, which were taken in an experiment made under the same conditions as the last, except

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that the rate of excitation was 80 per minute, instead of 23, as in the preceding experiment, and the record of every 50th contraction was recorded.
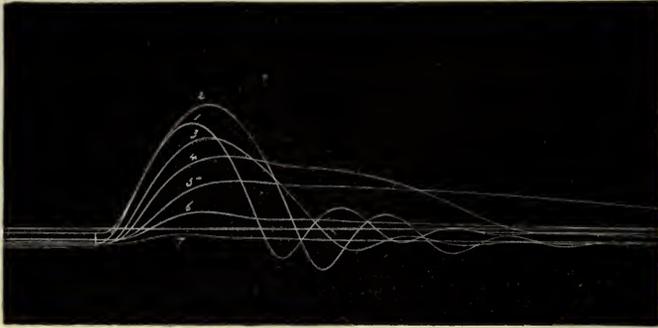
FIG. 45.—Effect of frequent excitation on the form of separate contractions. The method employed to obtain this record is the same as in the preceding experiment, except that the drum is revolving more rapidly, and every 50th contraction is recorded: 1 marks the first contraction; 2, the 50th: 3, the 100th; 4, the 150th; 5, the 200th; 6, the 250th; 7, the 300th.

A comparison of the first with the 50th contraction gives a number of points of interest. The stimulating effect of action upon the contraction process is shown by the fact that the latent period of the 50th (2 of Fig. 45) is shorter than that of the first, the rise of the curve is somewhat steeper, and the height is considerably greater. It is noticeable, however, that the crest is prolonged, and consequently the total length of the contraction is increased. In considering the greater activity of the contraction process of this 50th contraction as compared with the first, we must recall that it represents one of a series of staircase contractions, such as we noticed in Figure 43. If we examine the 100th contraction (3 of Fig. 45) we see the evidences of the beginning of fatigue; although the latent period is nearly as quick as in the first, the rise of the curve is less rapid, the height is less, and rate of relaxation is very much slowed. These changes are to be seen in a more marked degree in the 150th contraction (4 of Fig. 45), and the prolongation of the crest of the contraction and the decreased rate of relaxation are particularly noticeable. The same sort of differences are to be observed in the later contractions. By still more rapid rates of excitation these alterations in the contraction curve are not only exaggerated, but develop more quickly, and play a very important part in producing the peculiar form of continued contraction known as tetanus.

(3) *Effect of Frequent Excitations to Produce Tetanus.*—As we have seen, the normal muscle the first time that it is excited relaxes almost as quickly as it contracts, but if it be excited rhythmically a number of times a minute, gradually loses its power of rapid relaxation. The tendency to remain contracted begins to show itself in a prolongation of the crest of the contraction curve, even before fatigue comes on, and increases for a considerable time in spite of the effect of fatigue in lessening the height of the contractions. If a skeletal muscle of a frog be excited many times, at a rate of about once every two seconds, the gradual increase in the duration of the contractions will have the effect of preventing the muscle from returning to its normal length in the intervals be-

tween the succeeding stimuli, for contraction will be excited before relaxation is complete. As is shown in the record of the experiment reproduced in Figure 46, there will come a time in the work when the base-line connecting the lower extremities of the succeeding myograms will be seen to rise in the form of a curve, the change being at first gradual, then more and more rapid, and then again gradual (see *b*, Fig. 46). The effect of the change in the power to relax is to make it appear as if the muscle were the seat of two contraction processes, the one acting continuously, the other intermittently in response to the successive excitations. Such a condition as that exhibited in section *c*, Figure 46, is spoken of as an incomplete tetanus, complete tetanus being a condition of continuous contraction caused by rhythmical excitations, in which none of the separate contraction movements are visible. In complete tetanus the muscle writes an unbroken curve.
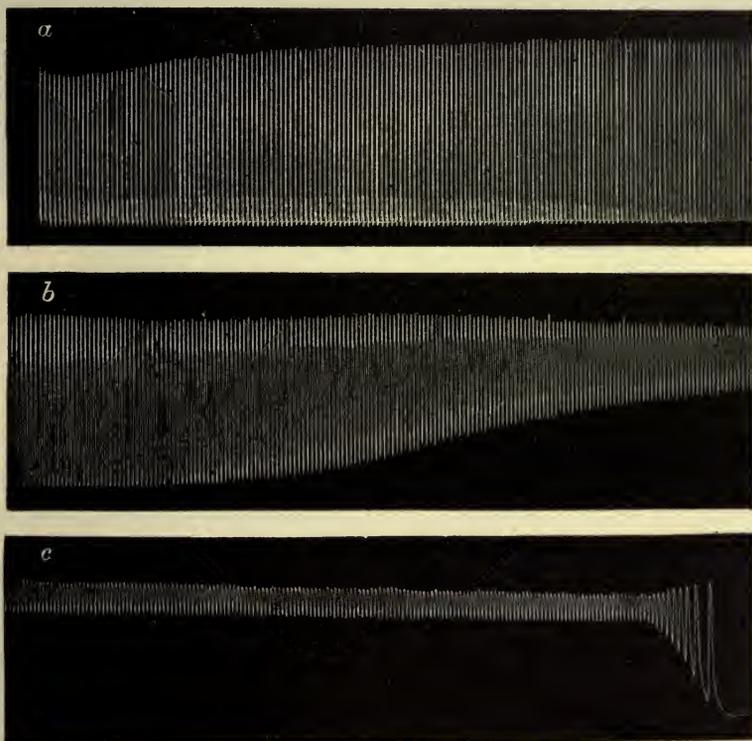
FIG. 46.—Effect of frequent stimuli to gradually produce incomplete tetanus. Series of isotonic contractions of a gastrocnemius muscle of a frog, excited once every two seconds by strong breaking induction shocks. Only a part of the record is shown, 70 contractions have been omitted between the end of the section marked *a* and the beginning of section *b*, and 200 contractions between the end of section *b* and the beginning of *c*. The increase in the extent of the relaxations seen at the close of the record was due to the slowing of the rate of excitations at that time.

The slowing of the relaxation of the muscle and consequent state of continued shortening which is to be seen in the latter part of the above experiment is termed "contracture." The amount of contracture increases, within limits, with the increase in the strength and rate of excitation. The intensity and

rate of stimulation required for the production of this condition depends very largely upon the character of the muscle, and its condition at the time.   In the experiment recorded in Figure 47 the development of the condition of con-
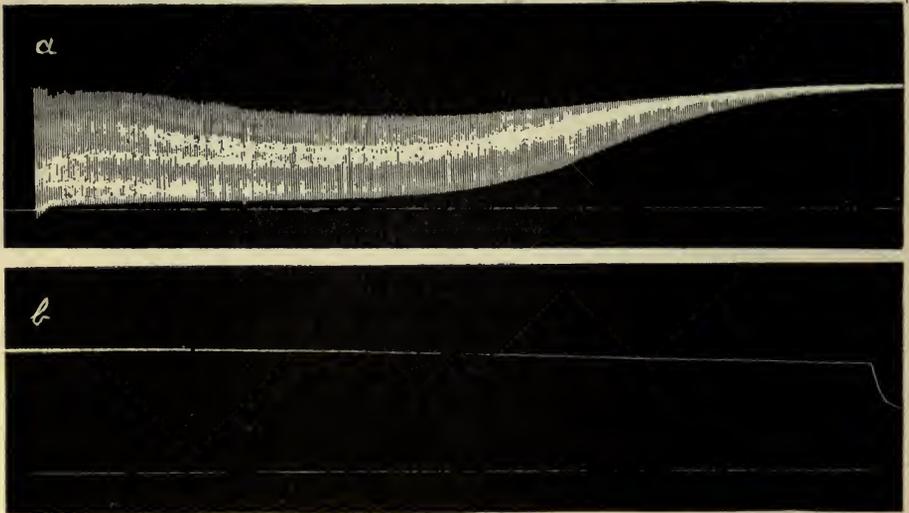
FIG. 47.—Effect of frequent excitations to gradually produce tetanus.   Experiment on a gastrocnemius muscle of a frog, similar to the last.   The weight was only 10 grams.   The rate of excitation was 100 per minute.   This muscle had been worked a short time before this series of contractions was taken, and, as a result, the introductory and staircase contractions were absent and contracture began much sooner than in the experiment recorded in Figure 45.   The record in section *b* is a continuation of that in section *a*.

tracture was more marked than in the above experiment, and the resulting condition of continued contraction caused first incomplete and finally complete tetanus.

Although frequent excitations appear to be essential to the development of contracture, it is doubtful whether it is to be considered a fatigue effect, since
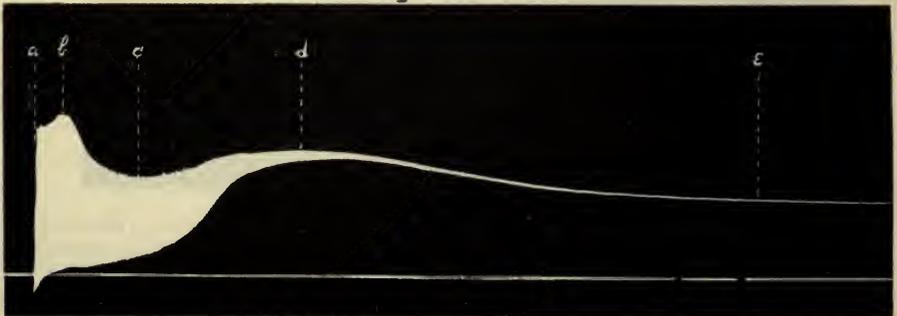
FIG. 48.—Development and fatigue of contracture.   Experiment on a gastrocnemius muscle of a frog. The weight was 10 grams.   As in the preceding experiments strong maximal breaking induction shocks were used to excite.   The rate of excitation was 5 per second.   The record appears as a silhouette for the reason that the drum was moving very slowly.

the contracted state which it produces may be increasing at the time that fatigue is lessening the height of the ordinary contraction movements, and since the

form of contraction peculiar to contracture is itself seen to lessen as fatigue becomes excessive. Both of these facts are illustrated in Figure 47, but are more strikingly shown in Figure 48, in which a more rapid rate of excitation was used.

The record in Figure 48 shows many points of interest : *a* to *b*, a rapidly developing *staircase*, which is accompanied by a rising of the base line, which indicates that contracture began to make itself felt from the moment the work began ; *b* to *c*, a rapid and then a gradual fall in the height of contractions due to *fatigue effects* ; *c* to *d*, a rise in the top of the curve in spite of the lessening height of the contractions, due to the increasing *contracture* ; *d* to *e*, a gradual fall of the curve of incomplete tetanus, due to the effect of *fatigue* on the contracture ; *e*, complete tetanus, but continued gradual *decline* in the height of the curve under the influence of fatigue.

The following experiment, Figure 49, differs from those which have preceded it, in that the muscle, instead of being directly excited, was stimulated indirectly by irritation of its nerve. Each shock applied to the nerve was represented by a separate contraction process in the muscle. The experiment illustrates well the combined effect of the *staircase* and the *contracture* to raise the height

FIG. 49.—Development of incomplete tetanus and contracture, by indirect stimulation. A gastrocnemius muscle of a frog was indirectly stimulated by breaking induction shocks, of medium strength, applied to the sciatic nerve. The rate was about 8 per second, as shown by comparison of the seconds traced at the bottom of the figure with the oscillations caused by the separate contractions. The weight was somewhat heavier than in the preceding experiment. The drum was revolving much faster than in the other experiments, hence the difference in the apparent duration of the contractions.

of the contractions. On account of the more rapid rate of excitation, the contracture came on more quickly than in the preceding experiments ; it did not become sufficient during the few seconds that this experiment lasted to prevent the separate relaxations from being seen, and an incomplete tetanus was the result.

In the experiment the record of which is given in Figure 50, the muscle was directly stimulated, and the rate of excitation was rapid, 33 per second. Not even this rate sufficed to cause complete tetanus, and the crest of the curve shows fine waves, which represent the separate contractions the combined effect of which resulted in the almost unbroken curve seen in the record. Had the rate been a little more rapid, no waves could have been detected and the tetanus would have been complete from the start. The effects of the staircase and contracture are merged into one another, and a very rapid high rise of the curve of contraction is the result. It is noticeable that the summit of the curve is rising throughout the experiment, owing to the increasing contracture.

It is evident that the condition of contracture which is developed in a
rapidly stimulated muscle will tend to maintain a condition of continuous con-

FIG. 50.—Effect of rapid excitations to produce tetanus. Experiment with a gastrocnemius muscle
of a frog, excited directly, with breaking induction shocks of medium strength, at the rate of 33 per
second. The weight was about 15 grams. The drum was moving much more slowly than in the pre-
ceding experiment. The time record gives fiftieths of a second.

traction, there being no opportunity for the muscle to relax in the intervals
between the succeeding excitations.

4. *Explanation of the Great Height of Tetanic Contractions.*—We have
now to seek an explanation of the fact that a muscle when tetanized will con-
tract much higher than it will as a result of a single excitation.   As we have
seen, repeated excitations cause, in the case of a fresh muscle, a gradual increase
in irritability and consequently a gradual rise in the height of the succeeding
contractions, but the staircase sooner or later reaches its upper limit, and will
not alone account for the great shortening which occurs in tetanus.

Effect of Two Rapidly Following Excitations.—Helmholtz was the first to
investigate the effect of rate of excitation on the height of combined contrac-
tions.   For the sake of simplicity, he excited a muscle with only two breaking
induction shocks, of the same strength, and observed the effect of varying the
interval between these two excitations.   He concluded that if the second stim-
ulus is given during the latent period of the first contraction, the effect is the
same as if the muscle has received but one shock ; if the second shock be applied
at some time during the contraction excited by the first, the second contraction
behaves as if the amount of contraction present when it begins were the resting
state of the muscle, *i. e.* the condition of activity caused by the first shock has
no influence on the amount of activity caused by the second, but the height
of the second contraction is simply added to the amount of the first contraction
present.   Were this rule correct, as a result of this summation, if the second
contraction occurred when the first was at its height, the sum of the two con-
tractions would be double the height of either contraction taken by itself.

Helmholtz' conclusion, that the condition of activity awakened by the first
excitation has no effect upon that caused by the second excitation, has not been
substantiated by later observers.   Von Kries[1] has found that the presence of
the first contraction hastens the development of the contraction process result-

[1] *Archiv für Anatomie und Physiologie*, 1888.

ing from the second excitation; and Von Frey[2] has ascertained that Helmholtz's rule of summation applies only to weighted muscles. In the case of unweighted muscles the summation effect is greatest when the second contraction starts during the period of developing energy caused by the first excitation, i. e. during the rise of the first contraction. If the second contraction
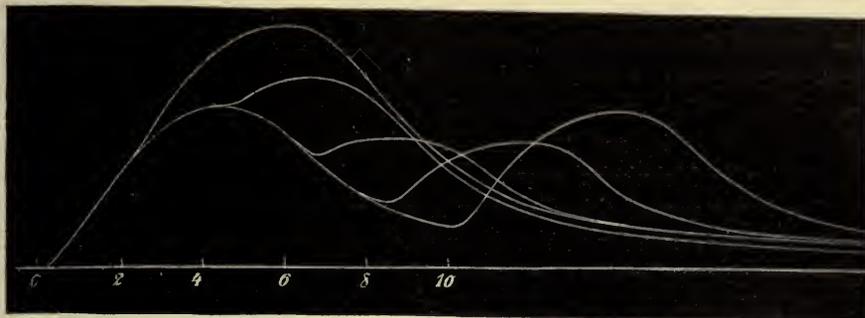
FIG. 51.—A schema of the effect of double excitations upon the gracilis muscle of a frog, by different intervals of excitation. To obtain this figure, the results of different experiments were superimposed (after Von Frey).

starts during the period of relaxation of the first, the second may be not even as high as when occurring alone (see Fig. 51).

The fact that the second contraction is higher if it starts during the ascent of the first, may be explained as due to a summation of the condition of ex-
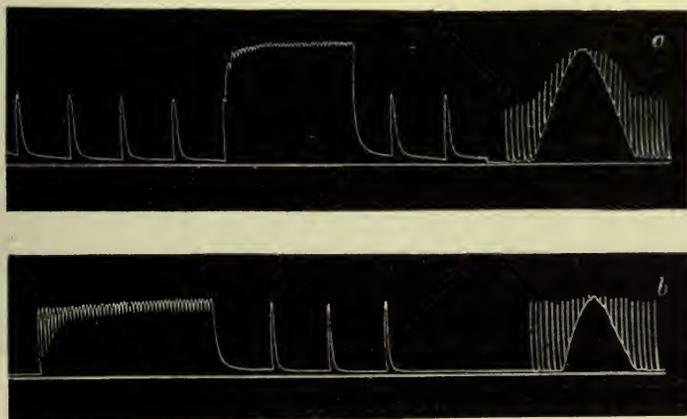
FIG. 52.—Effect of support on height of contractions (after Von Frey): a, gastrocnemius muscle of a frog, separate contractions, tetanus, separate contractions, and group of supported contractions; weight 10.5 grams; b, the same, by weight of 0.5 grams.

citation awakened by the two irritants, and hence the liberation of a greater amount of energy. Nevertheless, the increased irritability, indicated by staircase contractions, and the summation of excitation effects which occur by rapidly repeated excitations, shown by the above experiment, do not suffice to wholly explain the great shortening of the muscle seen in tetanus. Helmholtz' idea,

[1] *Archiv für Anatomie und Physiologie*, 1888, p. 213.

that there is a support afforded by the first contraction to the second, must also play an important part, and we must turn to this for the completion of the explanation of the great height acquired by the tetanus curve.

Effect of Support on the Height of Contractions.—Von Kries[1] and Von Frey[2] found that, in general, the shorter the distance the muscle has to raise a weight, the higher it can contract, and that if a muscle be excited at a regular rate, and the support for the weight be raised between each of the succeeding contractions, at a certain height of the support the contractions may be as high as during tetanus (see Fig. 52). This effect can be got with a fresh muscle when the interval between the excitations is such that there can be no summation in Helmholtz' sense.

The importance of this discovery to our understanding of tetanus is very great, for it has been found that if an unsupported muscle be rapidly excited, effects are observed which closely resemble those obtained by the aid of a sup-
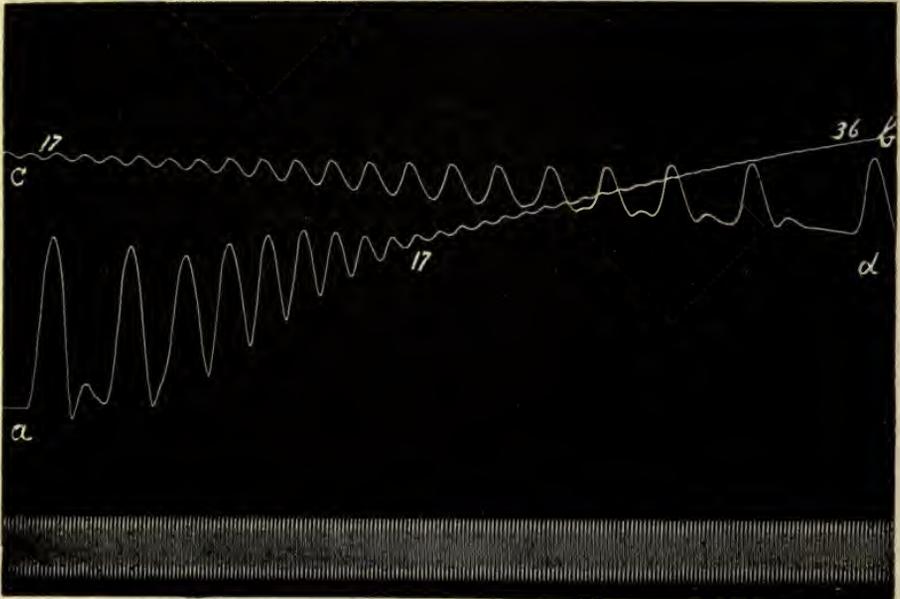
Fig. 53.—Effect of a gradually increasing rate of excitation. Excitation of a gastrocnemius muscle of a frog with breaking induction shocks of medium strength. The time was recorded directly, by a tuning-fork making 100 vibrations per second. The rate of excitation was gradually increased, and then gradually decreased. The ascending curve, *a–b*, shows the effect of increasing, and the descending curve, *c–d*, of decreasing the rate of stimulation. Excitation was given by means of a special mechanism for interrupting the primary circuit of an induction apparatus and at the same time short-circuiting the making shocks. This interrupter was run by an electric motor which was allowed to speed up slowly, and was slowed down gradually.

port; this we have seen in the experiments recorded in Figures 47, 48, p. 116. After a certain amount of excitation, a change occurs in the condition of a muscle, owing to which it acts as if it had received an upward push, and as if a new force had been developed within it, which aids the ordinary con-

[1] *Archiv für Anatomie und Physiologie,* 1886.
[2] *Ibid.,* 1887.

traction process in raising the weight. The new aid to high contraction is the support afforded by the developing condition of contracture.

5. *Effect of Gradually Increasing the Rate of Excitation.*—One of the most instructive methods of exciting tetanus is to send into the muscle a series of breaking induction shocks of medium intensity, at a gradually increasing rate. The record of such an experiment has been reproduced in Figure 53.

At the beginning of the experiment, *a*, one complete contraction with a wave of elastic after-vibration was recorded; this was followed by two contractions of less height, "introductory contractions;" then came three contractions each of which was higher than the preceding, "staircase contractions;" these were followed by three contractions, which, in spite of the developing contracture, were of less height, "fatigue effect." The rate of excitation at this place was about 17 per second. From this point on, the developing contracture supported the muscle more and more and the contraction waves became less and less, until finally, when the rate had become 36 a second, the effect of the separate stimuli could scarcely be detected, although the curve continued to rise. This is as far as the record shows, but the rate was increased still further, and the contraction curve continued to rise, although less and less, until finally an almost straight, unbroken line was drawn. After a little time this was seen to begin to fall, the contracture yielding to the effect of fatigue.

As the drum had nearly revolved to the place at which the experiment had been begun, the rate of excitation was then slowly decreased. With the lessening rate, the curve fell more and more rapidly, and oscillations began to show themselves. The character of the record during the rest of the experiment is shown in the curve *c–d*, Figure 53. At *c* the rate was about 17, and at *d* it was so slow that separate contractions were recorded, nevertheless the curve as a whole kept up. Indeed, even after the excitation had altogether ceased, the muscle maintained a partially contracted state for a considerable time, on account of the contracture effect, which only gradually passed off.

6. *Summary of the Effects of Rapid Excitation which produce Tetanus.*— Muscle-tetanus is the result of the combined action of a great many different factors, but the essential condition is that the muscle shall be excited at short intervals, so that the effect of each contraction shall have an influence on the one to follow it. This influence is exerted in several different ways: 1. Increase of irritability resulting from action, and leading to the production of staircase contractions; 2. Summation of excitation effects, as when each of the succeeding stimuli begins to act, before the contraction process excited by its predecessor has ceased; 3. Support given by the contracting muscle to itself, especially the support offered by contracture.

7. *Number of Excitations required to Tetanize.*—The number of stimuli per second required to tetanize a muscle depends largely on the nature of the muscle, for this decides the character of the separate contractions, and, through them, the effect of their combined action.

The duration of the separate contractions, and the tendency of the muscle to enter into contracture, are the predominant factors in determining the result.

Complete tetanus can only be obtained in the case of a fresh muscle, when the interval between succeeding stimuli is shorter than is required for the muscle to reach its maximal contraction by a single stimulus. Thus the prolonged contractions of smooth muscles permit of the development of a form of tetanus by successive closures of the galvanic current at intervals of several seconds. The contraction of some of the muscles of the turtle may last nearly a second, and two or three excitations a second suffice to tetanize. Tetanus of the red (slowly contracting) striated muscles of the rabbit can be obtained by 10 excitations per second, while 20–30 per second are required to tetanize the pale (active) striated muscles (Kronecker and Sterling). 100 stimuli per second are needed to tetanize the muscles of some birds (Richet), and over 300 per second would be required to tetanize the muscles of some insects (Marey). Strange to say, the heart-muscle cannot be tetanized; if it replies at all to frequent excitations, it gives the simple contractions characteristic of the heart-beat. Any influence which will prolong the contraction process will lessen the rate of excitation required to tetanize.

8. *Effect of Exceedingly Rapid Excitations.*—The question arises, Is there an upper limit to the rate of excitation to which muscles will respond by tetanus? There is no doubt that this is the case, but there is a difference of opinion as to what the limit is, and how it shall be explained.

Striated muscles and nerves can be excited by rates at which our most delicate chronographs fail to act. The muscle ceases to be tetanized by direct excitation at a rate by which it can still be indirectly excited through its nerve. The highest rate for the nerve has been placed at from 3000 to 22,000 by different observers,[1] and this wide difference is probably attributable to the methods of excitation employed. That such different results should have been reached is not strange, if we recall the many conditions upon which the exciting power of the irritant depends. As a rule, when the rate of excitation is so high that tetanus fails, a contraction is observed when the current is thrown into the nerve, and often another when it is withdrawn from the nerve. A satisfactory explanation for this, as well as for the failure of the tetanus, is at present lacking.

9. *Relative Intensity of Tetanus and Single Contractions.*—The amount that a muscle is capable of shortening, when tetanized by maximal excitations, and the strength of the tetanic contraction, depends very largely on the kind of muscle. For example, pale striated muscles, although capable of higher and more rapid single contractions than the red-striated, do not show as great an increase in the height and strength of contractions when tetanized as do the red; the latter, which are very rich in sarcoplasma, have likewise the greater endurance. Gruetzner has called them "tetanus muscles," since they seem to be particularly adapted to this form of contraction. Fick found that human muscles when tetanized develop ten times the amount of tension, by isometric

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[1] Kronecker and Sterling: *Archiv für Anatomie und Physiologie,* 1878, and *Journal of Physiology,* 1880, vol. i. Von Frey und Wiedermann: *Berichte der sächsischen Gesellschaft der Wissenschaft,* 1885. Roth: *Pflüger's Archiv,* 1888.

contractions, that they give by single contractions; and in this respect they can be said to resemble red striated muscles. The following relations have been found to exist between separate contractions and tetanus in certain muscles: triceps and gastrocnemius of the frog, 1 : 2 or 3; the corresponding muscles of the turtle, 1 : 5; hyoglossus and rectus abdominalis of the frog, 1 : 8 or 9.[1] It is evident that no just estimate of the part played by different groups of muscles in the movement of the body can be reached without a careful analysis of the nature of the contractions peculiar to each of the muscles participating in the movement.

Both the height and strength of the tetanus is controlled by the intensity of the stimulus. A strong stimulus not only causes the separate contractions of which the tetanus is composed to be higher, but is favorable to the development of all the other factors which have been described as entering into the production of tetanus. All normal physiological contractions are supposed to be tetani, and everyone is conscious of the wonderful accuracy with which he can grade the extent and strength of his voluntary movements. The remarkable shading of the intensity of action observable in co-ordinated movements must find its explanation in the adjustment of protoplasmic activity in the nerve-cells of the central nervous system.

10. *Continuous Contractions caused by Continuous Excitation.*—Attention has been already called to the fact that under certain circumstances a form of continuous contraction may be excited by a continuous constant electric current. If the current be very strong, the short closing contraction may be followed by a more or less continuous contraction—the closing (or Wundt's) tetanus, and the short opening contraction may be followed by another continuous contraction, which only gradually passes off—the opening (or Ritter's) tetanus. This form of contraction is quite readily excited in normal human muscles, both by direct and indirect excitation. The term "galvanotonus" is sometimes employed for the continuous contraction of human muscles excited by the continuous flow of a constant current.

The closing tetanus originates at the kathode, and the opening tetanus at the anode. The contraction process may spread rapidly from the point of origin to the rest of the muscle, or, if the muscle be in an abnormal state, or be dying, the contraction may remain localized as a circumscribed swelling, or welt. Although a continuous contraction caused by the constant current is spoken of as tetanus, it is a matter of doubt whether it is a true tetanic condition, for the term tetanus is limited to an apparently continuous contraction resulting from many frequently repeated stimuli. Von Frey[2] expresses the view that the continuous contraction which follows the closing of the continuous constant current is a form of tetanus. It is certainly true that the closing tetanus often shows irregular oscillations, suggestive of a more or less intermittent excitation. This might be attributed to irregular chemical changes produced in the muscle-substance by the electricity and leading to irregular

[1] Biedermann: *Elektrophysiologie*, p. 109.
[2] *Archiv für Anatomie und Physiologie*, 1885, p. 55.

contractions of the different fibres, the combined action of which produces a more or less regular continued contraction. Another view would be that contracture might be produced under the influence of the changes caused by the electric current, and a condition result similar to that which causes the prolonged contractions which are characteristic of poisoning with veratria, etc. (see p. 128).

(d) *Normal Physiological Contractions.*—All normal physiological contractions of muscles are regarded as tetani. Even the shortest possible voluntary or reflex movements are considered to be too long to be single contractions. Inasmuch as we can artificially excite muscles to continuous contraction only by means of a series of rapidly following stimuli, we find it hard to explain continuous contractions on any other basis, and hence the view that the excitation sent by the nerve-cells to muscles has always a rhythmic character, and that the normal motor-nerve impulse is a discontinuous rather than continuous form of excitation. The view is probably correct, but cannot be considered as proved. The evidence in favor of it is as follows.

Muscle-sounds, Tremors, etc.—During voluntary muscular contractions the muscle gives out a sound, which would imply that its finest particles were not in a state of equilibrium, but vibrating. By delicate mechanisms it has been possible to obtain records of voluntary and reflex contractions which showed oscillations, although the contraction of the muscle appeared to the eye to be continuous. If the surface of a muscle be exposed and be wet and glistening, the light reflected from it during continued contractions is seen to flicker, as if the surface were shaken by fine oscillations. The tired muscle passes from apparently continuous contraction to one exhibiting tremors, and muscular tremors are observed under a variety of pathological conditions.

With these facts in mind, a number of observers have endeavored to discover the rate at which the muscle is normally stimulated. Experiments in which muscles have been excited to incomplete tetanic contractions by induced currents, interrupted at different rates, have shown that the muscle follows the rate of excitation with a corresponding number of vibrations, and does not show a rate of vibration peculiar to itself. Further, it has been ascertained that the sound given out by a muscle excited to complete tetanus, *i. e.* an apparently continuous contraction, corresponds to the rate at which it is excited. Apparently, any rate of oscillations detected in a muscle during normal physiological excitation would be an indication of the rate of discharge of impulses from the central nerve-cells.

Wollaston was the first to observe that a muscle gives a low dull sound when it is voluntarily contracted, and that this sound corresponds to a rate of vibration of 36 to 40 per second. It may be heard with a stethoscope placed over the contracting biceps muscle, for instance, or if, when all is still and the ears are stopped, one vigorously contracts his masseter muscles. Helmholtz placed vibrating reeds consisting of little strips of paper, etc., on the muscle, and found that only those which had a rate of vibration of 18 to 20 per second were thrown into oscillation when the muscle was voluntarily contracted.

This observation indicated that the muscle had a rate of vibration of 18 to 20 per second, a rate too slow to be recognized as a tone. He concluded that the tone heard from the voluntarily contracted muscle was the overtone, instead of the true muscle-tone. The consideration that the resonance tone of the ear itself corresponds to 36 to 40 vibrations per second, makes it questionable whether the muscle-sound should be accepted as evidence of the rate of normal physiological excitation; nervetheless, the experiments with the vibrating reeds remain to indicate 18 to 20 per second to be the normal rate.

Within the last few years a number of researches bearing upon this question have been published, and the results of these point to a still slower rate of voluntary excitation, varying from 8 to 12 per second according to the muscle on which the experiment is made. Lovén[1] discovered in the tetanus excited in frogs poisoned with strychnia, and in voluntary contractions, both by mechanical methods and by recording the electrical changes occurring during action with the capillary electrometer, rates of 7 to 9 per second. Horsley and Schafer[2] excited the brain cortex and motor tracts in the corona radiata and the spinal cord of mammals by induction shocks, at widely differing rates, and recorded the resulting muscular contractions by tambours placed over the muscles. They observed oscillations in the myograms obtained which had a rate of 8 to 12 per second, the average being 10. The rate of oscillations was quite independent of the rate of excitation, and oscillations of the same rate were seen by voluntary and by reflex contractions. Tunstall[3] found by the use of tambours, in experiments on voluntary contractions of men, a rate of 8 to 13 per second, with an average of 10. Griffiths[4] likewise used the tambour method, and studied the effect of tension on the rate of oscillations in voluntarily contracted human muscles. He observed rates varying from 8 to 19, the rate being increased with an increase of weight up to a certain point, and beyond this decreased. The oscillations became more extensive as fatigue developed. Von Kries by a similar method found rates varying with different muscles, but averaging about 10.

It is not easy to harmonize the view that 8 to 13 excitations per second can cause voluntary tetani, when it is possible for the expert pianist to make as many as 10 or 11 separate movements of the finger in a second. It is, indeed, a common observation that a muscle can be slightly and continuously voluntarily contracted, and, at the same time, be capable of making additional short rapid movements. Von Kries would explain this as due to a peculiar method of innervation, while Biedermann favors Gruetzner's[5] view that the muscle may contain two forms of muscle-substance, one of which is slow to react, resembling red muscle-tissue, and maintains the continuous contraction, the other, of more rapid action, being responsible for the quicker movements. Although the evidence is, on the whole, in favor of the view that all normal

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[1] *Centralblatt für medicinische Wissenschaft*, 1881. [2] *Journal of Physiology*, 1886, vii. p. 96.
[3] *Journal of Physiology*, 1886, vii. p. 114. [4] *Journal of Physiology*, 1888, ix. p. 39.
[5] *Pflüger's Archiv*, 1887, Bd. 41, S. 277.

contractions of voluntary muscles are tetanic in character, there is a great deal which remains to be explained.

Effect of Artificial compared with Normal Stimulation.—Experiment shows that, with the same strength of irritant, a muscle contracts more vigorously when irritated indirectly, through its nerve, than when it is directly stimulated. Rosenthal describes the following experiment : If the nerve of muscle A be allowed to rest on a curarized muscle B, and an electric shock be applied in such a way as to excite nerve A and muscle B to the same amount, muscle A will be found to contract more than muscle B.

Further, it has been found that muscles respond more vigorously to voluntary excitations than to any artificial stimulus which can be applied to either the nerve or muscle. This shows itself, not only in the fact that a muscle can by voluntary stimulation lift much larger weights than by electrical excitation, but that after a human muscle has been fatigued by electrical excitations it can still respond vigorously to the will. An illustration of this is given in Figure 54.
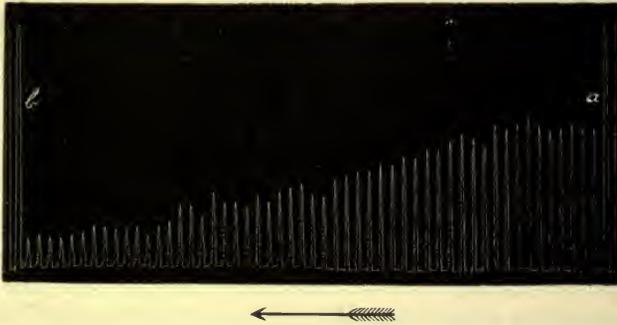
Fig. 54.—Voluntary excitations are more effective than electrical. The flexor muscles of the second finger of the left hand of a man were excited first voluntarily, *a*, then electrically, *a-b*, and then voluntarily, *b*. The electrical excitation consisted of series of induction shocks, which were applied once every two seconds, during about half a second, the spring interrupter of the induction coil vibrating 23 times per second. Each time the muscle contracted it raised a weight of one kilogram. Each of the contractions recorded, whether the result of electrical or voluntary excitation, was a short tetanus.

Fatigue of Voluntary Muscular Contractions.—Mosso and his pupils have done a large amount of work upon the fatigue of human muscles when excited by voluntary and artificial stimuli under varying conditions. The results at which they arrived all favor the view that human muscles differ but little from those of warm-blooded animals, and that the facts which have been ascertained by experiments upon cold-blooded animals, such as the frog, can be accepted with but slight modifications for the muscles of man. In the experiment recorded in Figure 55 we see the effect of repeated tetanic contractions, excited by electricity, to fatigue a human muscle. Normal voluntary contractions, if frequently repeated, provided the muscle has to raise a considerable weight, likewise cause fatigue.

It is doubtful whether, in an experiment such as is shown in Figure 55, the loss of the power to raise the weight is due to fatigue of the muscles. It is more likely that the decline in power is really due to fatigue of the central

nerve-cells by which the muscles are excited to action during voluntary muscular work.[1] This fact, that the nerve-cells give out before the muscles, explains the apparent contradiction, that a muscle fatigued by electric excitations can be voluntarily contracted, and when the power to voluntarily contract the
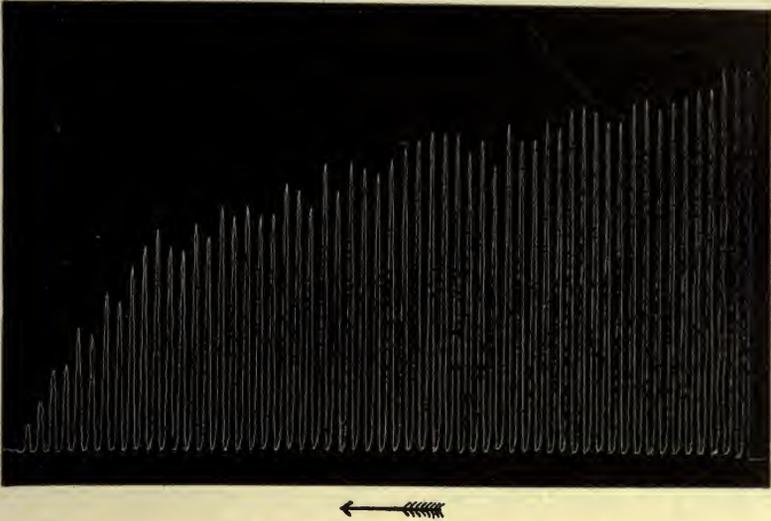
FIG. 55.—Effect of fatigue on voluntary muscular contractions. The flexor muscles of the second finger of left hand were voluntarily contracted once every two seconds, and always with the utmost force. The weight raised was four kilograms.

muscles has been stopped by fatiguing voluntary work the muscles will respond to electrical excitation. It is undoubtedly of advantage to the body that the nerve-cells should fatigue before the muscles, for the muscles are thereby protected from the injurious effects of overwork, and are always ready to serve the brain.[2] It may be added that nerve-cells not only fatigue more quickly, but recover from fatigue more rapidly than the muscles.

(e) *Effect of Temperature upon Muscular Contraction.*—Heat, within certain limits, increases the irritability and conductivity of muscle-tissue, and at the same time has a favoring influence upon those forms of chemical change which liberate energy. The effect of a rise of temperature, as shown by the myogram, is a shortening of the latent period, an increase in the height of contraction, and a quickening of the contraction and relaxation, the whole curve being shortened. Of course there is an upper limit to this favoring action, since, at a certain temperature, about 45° C. for frog's muscle and about 50° C. for the muscles of warm-blooded animals, heat-rigor begins, and this change is accompanied by a loss of all vital properties. Cold can be said, in general, to produce effects the opposite of those of heat; as the muscle is cooled, the latent period, the contraction, and the relaxation, are all prolonged.

Nevertheless, the effect of temperature is not a simple one (see Fig. 56). If

[1] Lombard : *Archives Italiennes de Biologie,* xiii. p. 1; or *American Journal of Psychology,* 1890, p. 1; *Journal of Physiology,* 1892, p. 1; 1893, p. 97.

[2] Waller : *Brain,* 1891, p. 179.

during the cooling process a striated muscle of a frog be irritated from time to time with single induction shocks, the height of the contractions does not continually grow less as one would expect.[1]   The maximal height is obtained at 30° C., the height above this point being somewhat less, the irritability lessening as the coagulation-point is approached; from 30° C. to 19° C. the height continually decreases, but from 19° to 0° C. the height increases, while below 0° C. it again becomes less, until at the freezing-point of muscle no contraction is obtained.   The cause of these peculiar phenomena is not definitely understood.
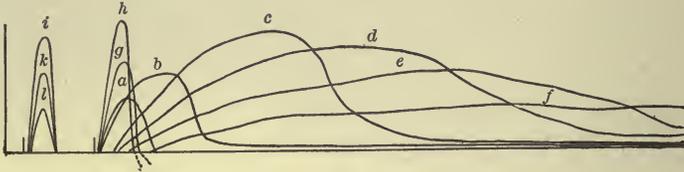
FIG. 56.—Schema of effect of temperature on height and form of contraction curve: *a*, contraction at 19° C.; *b, c, d, e, f*, contractions made at intervals, each one at a lower temperature; *g, h*, contractions at higher temperatures than 19° C., *h* being made when the temperature was 30° C.; *i, k, l*, show a different series of contractions, made as the temperature was increased from 30° C. toward the point at which the muscle-substance coagulates (after Gad and Heymans).

(f) Effect of Drugs and Chemicals upon Muscular Contraction.—Certain drugs and chemicals have a marked effect upon the irritability and conductivity of muscles, and these effects must necessarily find expression in the amount of contraction which would be excited by a given irritant.   In addition to this, it is worthy of notice that the character of the contraction may be altered.

The drug which has the most striking effect upon the form of contraction is veratria.   A few drops of a one per cent. solution of the acetate of veratria, injected beneath the skin of a frog whose brain has first been destroyed, in a few minutes alters completely the character of the reflex movements; the muscles
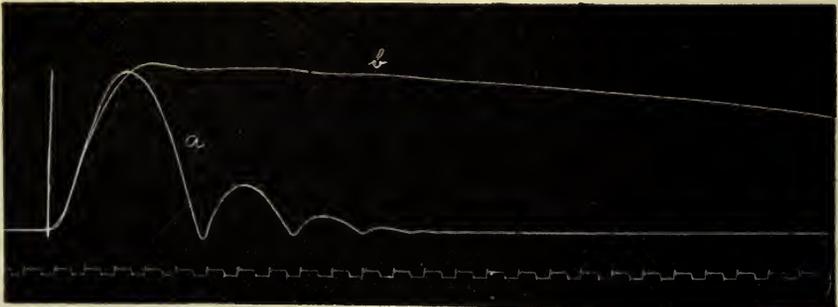
FIG. 57.—Myogram of muscle poisoned with veratria and that of a normal muscle: *a*, myogram from a normal gastrocnemius muscle of a frog—the waves at the close are due to the recoil of the recording lever; *b*, myogram from a gastrocnemius muscle poisoned with veratria, recorded at the same part of the drum.

are still capable of rapidly contracting, but the contractions are cramp-like, the power to relax being greatly lessened.   The poison acts upon the muscle-substance.   If a muscle poisoned with veratria be isolated and connected with

[1] Gad und Heymans: *Archiv für Anatomie und Physiologie*, 1890, p. 73.

a myograph, a contraction excited by a single induction shock will show a rise as rapid and as high as normal, but the fall of the curve will be greatly prolonged (see Fig. 57).

Often the crest of the curve will exhibit a notch, which shows that relaxation may begin and be checked by a second contraction process which carries the curve up again and holds it there for a considerable time. In the above experiment the contracture effect followed the primary contraction immediately.

If the muscle be frequently excited, the characteristic prolongation of the contraction disappears, and the curve becomes normal; but if the muscle be allowed to rest, there is a return of the condition. Both high and low temperatures act like exercise to prevent this peculiar effect of veratria from showing itself.

Barium salts, and to a less degree calcium and strontium, act similarly to veratria to prolong the relaxation of the muscle without lessening the rapidity and height of the contraction. Potassium and ammonium salts act to kill the muscle, and, as the death-process develops, excitation produces prolonged localized contractions. This effect seems to be quite different from that of veratria, being accompanied by a rapid lessening of the power of the muscle. Sodium salts in strong solution may increase the irritability and induce fatigue, which is always accompanied by a prolongation of the curve of relaxation.

The condition of continued contraction caused by veratria is a form of " contracture." The true nature of the condition is still under discussion; the fact that the veratria contracture passes off if the muscle is worked, shows that it is not in the nature of a fatigue effect. Since more heat is produced during contracture than during rest (Fick and Boehme), it is to be regarded as an active contraction process and not an increase of elasticity. The fact that the crest of the veratria curve often exhibits a notch, and that the second rise, leading to the prolonged ridge, may be higher than the primary rise, has been interpreted to mean that the muscle contains two different forms of muscle-tissue which, like the pale (rapid) and red (slower) striated muscles of the rabbit, have different rates of contraction. The first rise is supposed to be due to the quicker and the second to the slower form of muscle. A similar double crest is seen in the contraction curves of muscles the irritability of which has been heightened by sodium carbonate, and indeed in the curves from muscles of normal frogs after their irritability has been increased by frequent excitations.

Liberation of Energy by the Contracting Muscle.—The law of conservation of energy applies no less to the living body than to the inanimate world in which it dwells. Every manifestation of life is the result of the liberation of energy which was stored in the body in the form of chemical compounds. When a muscle is excited to action it undergoes chemical changes, which are accompanied by the conversion of potential to kinetic energy. This active energy leaves the muscle in part as thermal energy, in part as mechanical energy, and, to a slight extent, under certain conditions, as electrical energy. In general, the sum of the liberated energy is given off as heat

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or motion. The proportion in which these two forms of energy shall be produced by a muscle may vary within wide limits, according to the state of the muscle and the conditions under which the work is done. Fick [1] states that if the muscle works against a very heavy weight, possibly $\frac{1}{4}$ of the liberated energy may be obtained as mechanical work, but if the weight be light not more than $\frac{1}{20}$ of the chemical energy is given off in this form, the muscle working no more economically than a steam engine. The fact that always a part, and often the whole, of the mechanical energy developed by the muscle is converted to thermal energy within the muscle, and leaves it as heat, makes it the more difficult to determine in what proportion these two forms of energy were originally produced. Moreover, if Engelmann's view be correct, that the change of form exhibited by the muscle is the result of the imbibition of the fluid of the isotropic substance by the anisotropic material, this change being brought about by the heat which is liberated within the muscle, we must consider potential energy to be set free first as heat, a part of which is afterward changed to mechanical energy, which in part, at least, is again changed to heat.

Liberation of Mechanical Energy.—In estimating the amount of mechanical energy liberated by a muscle, we observe the amount of physical work which it accomplishes, *i. e.* the amount of mechanical energy which it imparts to external objects. If a muscle by contracting raises a weight, it gives energy to the weight, the amount being exactly that which the weight in falling through the distance which it was raised by the muscle can impart as motion, heat, etc., to the objects with which it comes in contact. The measure of the mechanical work done by the contracting muscle is the product of the weight into the height to which it is lifted. For example, if a muscle raises a weight of 5 grams, 10 millimeters, it does 50 grammillimeters of work.

The amount of work which a muscle can do depends on the following conditions :

(*a*) *The kind of muscle.* The muscles of warm-blooded animals are stronger than those of cold-blooded animals; a human muscle can do two to three times the amount of work of an equal amount of frog's muscle. The muscles of certain insects have even greater strength.[2]

(*b*) *The quantity of muscle-substance and the arrangement of the fibres.* The power of a muscle to do mechanical work, the absolute muscular force, is estimated by the weight which, brought upon the muscle at the instant it begins to contract, prevents it from shortening but does not stretch it, *i. e.* one which exactly balances the contractile force of the muscle when it is excited to a maximal tetanic contraction. It is evident that the amount of force which can be developed will depend on the amount of contractile substance and on the arrangement of the fibres. Since the force which can be developed by a contracting muscle depends largely on the arrangement of the microscopic contractile mechanisms of which it is composed, it is found best, for purposes of compari-

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[1] Fick: *Pflüger's Archiv*, 1878, xvi. p. 85.
[2] Hermann : *Handbuch der Physiologie*, 1879, Bd. i. p. 64.

son, to state the strength of a muscle and its capacity to do work, for the unit of bulk, one cubic centimeter, or the unit of weight of muscle-substance, one gram. Thus, the absolute muscular force of frog's muscle is estimated to be about 3 kilograms per cubic centimeter, and of human muscle to be 8 to 10 kilograms per cubic centimeter. Fick states that the maximal amount of external work of which frog's muscle is capable is 1 grammeter per gram of muscle-substance.

(c) *The condition of the muscle.* Any of the influences which lessen the irritability of the muscle—lack of blood, fatigue, cold, etc.—decreases the power to liberate energy, and any influence which heightens the irritability is favorable to the work. The effect of tension to heighten irritability has already been referred to and is of especial interest in this connection, since the very resistance of the weight is, within limits, a condition favorable to the liberation of the energy required to overcome the resistance. This will be referred to again.

(d) *The strength and character of the stimulus.* The liberation of energy is, up to a certain point, the greater, the stronger the excitation. Furthermore, rapidly repeated excitations are much more effective than single excitations, because a series of rapidly following stimuli, both by altering the irritability and by inducing the form of contraction known as tetanus, act to produce powerful and high contractions. Bernstein states that the energy developed by the muscle increases with the increase of the rate of excitation from 10 to 50 per second, at which rate the contraction power may be double that called out by a single excitation.

(e) *The method of contraction and the mechanical conditions under which the work is done.* Inasmuch as mechanical work is measured by the product of the weight into the height to which it is lifted, an unweighted muscle in contracting does no work; a muscle, however vigorously it may contract, if it be prevented from shortening, does no work; finally, a muscle which raises a weight and then lowers it again when it relaxes, does not alter its surroundings as the tot result of its activity, and hence does no work. Although no mechanical work is accomplished under these circumstances, physiological work is being done, as is evidenced by the fatigue produced. Unquestionably mechanical energy is developed within the muscle in all these cases, but it is all converted to heat before it leaves the muscle.

The amount of weight is an important factor in determining the extent to which a muscle will shorten when excited by a given stimulus, and, therefore, the quantity of work which it will accomplish. If a muscle be after-loaded, *i. e.* if the weight be supported at the normal resting length of the muscle, and the muscle be excited to a series of maximal contractions, the weight being increased to a like amount before each of the succeeding excitations, there is, in general, a gradual lessening in the height of the contractions, but the decrease in height is not proportional to the increase of the weight. The decrease in the height of contractions is, as a rule, more rapid at the beginning of the series than later, though at times an opposite tendency may show itself

and the increasing weights temporarily increase the irritability and therefore increase the amount of shortening. The effect of tension to increase the activity of the contraction process is seen if a muscle which is connected with a strong spring or heavy weight be excited to isometric contractions and in the midst of a contraction be suddenly released; the muscle under such circumstances is found to contract higher than when excited by the same stimulus without being subjected to tension. The effect of tension on the activity of muscular contractions is to be clearly seen in the case of the heart muscle. A rise of pressure of the fluid within the isolated heart of a frog increases the strength as well as the rate of the beat.

If the weight be gradually increased, although the height of the contractions is lessened, the work will for a time increase, and a curve of work (constructed by raising ordinates of a length corresponding to the work done, from points on an abscissa at distances proportional to the weights employed), will be seen to rise. After the weight has been increased to a certain amount the decline in the height of contractions will be so great that the product of the weight into the height will begin to decrease, and the curve of work will fall, until finally a weight will be reached which the contracting muscle can just support at, but not raise above, its normal resting length. As has been said, this weight will be a measure of the absolute muscular force.

Example.

Load (grams).	Height of lift (millimeters).	Work (grammillimeters).
0	13	0
30	11	330
60	9	540
90	7	630
120	5	600
150	3	450
180	2	360
210	0	0

In the above experiment 30 grams was added to the muscle after each contraction; as the weight was increased up to 90 grams the amount of work was increased, with greater weights the amount of work was lessened.

Liberation of Thermal Energy.—Energy leaves the body as mechanical energy only when by its movements the body imparts energy to surrounding objects. Most of the energy liberated within the body leaves it as heat; even during violent muscular exercise five times more energy may be expended as heat than as mechanical energy, and the disproportion may be even greater than this. So great is the production of heat during exercise, that, in spite of the great amount leaving the body, the temperature of an oarsman has been found to be increased, during a race of 2000 meters, from 37.5° C. to 39° or 40° C.[1]

It is exceedingly difficult to ascertain with accuracy on the warm-blooded animal the exact relation of heat-production to muscular contraction. The

[1] Geo. Kolb: *Physiology of Sport*, translated from the German, 2d edition, London, 1892.

best results have been obtained by experiments on isolated muscles of cold-blooded animals. Helmholtz observed the temperature of a muscle of a frog to be increased by tetanus lasting a couple of minutes 0.14° to 0.18° C.; Heidenhain saw a change of 0.005° C. result from a single contraction; and Fick ascertained that a fresh, isolated muscle of a frog can by a single contraction produce per gram of muscle-substance enough heat to raise 3 milligrams of water 1° C.[1] To obtain evidence of the slight changes of temperature which occur in such small masses of muscle-tissue it is necessary to employ a very delicate instrument, such as a thermopile or a bolometer.

The thermopile consists of strips of two dissimilar metals, united at their extremities, so as to form a series of thermo-electric junctions. If there be a difference of temperature at two such junctions, a difference of electric potential is developed, which causes the flow of an electric current. If the current be passed through the coils of wire of a galvanometer its amount can be measured, and the extent of the change in temperature at one of the junctions, the other remaining constant, can be estimated. In the more sensitive instruments, several thermo-electric junctions are used. The amount of current depends largely on the metals employed, antimony and bismuth being a very sensitive combination.

The action of the bolometer is based on the fact that the resistance of a wire to the passage of an electric current changes with its temperature.

The amount of heat developed within the muscle by direct conversion of potential to thermal energy, and the amount formed indirectly, through conversion of mechanical to thermal energy, has been made a subject of careful study by Heidenhain,[2] Fick and his pupils,[3] and others, the experiments being made chiefly with isolated muscles of frogs.

In general, the stronger the stimulus and the greater the irritability of the muscle—in other words, the more extensive the chemical changes excited in the muscle—the greater the amount, not only of mechanical, but of thermal energy liberated. Increase of tension, which is very favorable to muscular activity, greatly increases the heat-production. As the weight is increased, both the amount of heat developed and the work are increased, but the liberation of heat reaches its maximum and begins to decline sooner than the amount of work, *i. e.* with large weights the muscle works more economically; similarly, as the muscle is weakened by fatigue the heat-production lessens sooner than the work.

Muscle-tonus and Chemical Tonus.—During waking hours, the cells of the central nervous system are continually under the influence of a shower of weak nervous impulses, coming from the sensory organs all over the body;[4] moreover, activity of brain-cells, especially emotional forms of activity, leads

[1] Fick: *Pflüger's Archiv*, 1878, xvi. p. 89.

[2] *Mechanische Leistung, Wärmeentwicklung und Stoffumsatz bei der Muskelthätigkeit*, Leipzig, 1864.

[3] *Myothermische Untersuchungen aus den physiologischen Laboratorium zu Zürich und Wurzburg*, Wiesbaden, 1889.

[4] Brondgeest: *Archiv für Anatomie und Physiologie*, 1860, p. 703; Hermann, *Ibid.*, 1861, p. 350.

to an overflow of nervous impulses to the spinal cord and an increased irritability, or, if stronger, excitation of motor nerve-cells. If, when one is quietly sitting and reading, he turns his attention to the sensory impressions which are coming at every moment from all over the body to the brain, notes the temperature of different parts of the skin, the pressure of the clothes, etc., upon different parts, the light reflected from neighboring objects, and the slight sounds about him, he will recognize that the central nervous system is all the time subject to a vast number of excitations, which, because of their very repetition, are ordinarily disregarded by the mind, but which are, nevertheless, all the time influencing the nerve-cells. The effect of this multitude of afferent stimuli, in spite of their feebleness, is to cause the motor cells of the cord to continually send delicate motor stimuli to the muscles. These cause the muscle to keep in the state of slight but continued contraction which gives the tension peculiar to waking hours, and which is called *muscle-tonus.* That such a tension exists is made evident by the change in attitude which occurs when the relaxation accompanying sleep comes on. The effect of brain activity to cause muscular tension is, likewise, most easily recognized by observing the relaxation of the muscles which occurs when mental excitement ceases.

Muscle-tonus, like every form of muscular contraction, is the result of chemical change, and the liberation of energy. But little of this energy leaves the body as mechanical energy, most of it being given off as heat.

This view is by no means universally accepted, and many physiologists believe in a production of heat by the muscles, as a result of nervous influences, independent of contraction. It is thought that a condition of slight but continuous chemical activity resulting in the production of heat may be maintained in the muscles by intermittent but frequent reflex excitations, a condition which has been called *chemical tonus.*[1] That the chemical activity of muscles is kept up by small stimuli from the spinal cord is shown by the fact that if the nerves be severed, or the nerve-ends be poisoned by curare, the muscle absorbs less oxygen and gives off less carbon dioxide than when at rest under normal conditions.[2]

The theory of a reflex chemical tonus independent of contraction implies the existence of special nervous mechanisms for the exciting of chemical changes in the muscles which shall result in the liberation of energy as heat, independent of the change of form of the muscle. The question of the existence of special nervous mechanisms controlling heat-production—heat-centres, as they are called—will be considered in another part of this book.

E. ELECTRICAL PHENOMENA IN MUSCLE AND NERVE.

The active muscle liberates three forms of energy : mechanical work, heat, and electricity. The active nerve makes no visible movements, gives off no recognizable quantity of heat, but exhibits changes in electrical condition quite

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[1] Roehrig und Zuntz : *Pflüger's Archiv,* 1871, Bd. iv.; Pflüger: *Pflüger's Archiv,* 1878, xviii. p. 247.

[2] Zuntz : *Pflüger's Archiv,* 1876, xii. 522; Colasanti, *Ibid.,* 1878, xvi. p. 57.

comparable to those observed in the active muscle. The electrical changes in nerves are the only evidence of activity which we can observe, aside from the effect of the nerve on the organ which it excites; they are therefore of great interest to us.

Electrical energy, like all forms of active energy, is the result of a transformation of potential or some form of kinetic energy. In the case of the muscle, as of an electric battery, we find electricity to be associated with chemical change, and believe it to be liberated from stored potential energy. In the case of nerves no chemical change can be detected during action, and hence we are at a loss to explain the devolopment of electricity. We can only say that it is the result of some chemical or physical process which we have as yet failed to discover.

Although activity of nerve and muscle is found to be associated with electrical change, we must not suppose functional activity to be in any sense an electrical process. The movements of a man may be interpreted from the movements of his shadow, but they are very different phenomena; the activity of the nerve and muscle is indicated by the electrical changes accompanying it, but they may be independent processes. Certainly the irritating change which is transmitted along the nerve and which excites the muscle to action, although accompanied by electrical changes, is not itself an electric current.

Electrical energy is exhibited not only by active nerve and muscle, but during the activity of a great variety of forms of living matter. It may be detected in gland-cells, in the cells of many of the lower animal organisms, and even plant-cells. The amount of electrical energy developed in animal tissues may be far from trivial. Although delicate instruments are necessary to observe the electrical changes in nerve and muscle, as the great internal resistance of the tissues causes the currents to be small, we find in certain fish special electric organs, which appear to be modified muscle-tissue, and which are capable of discharging a great amount of electrical energy when excited through their nerves. So intense is the action of this electrical apparatus that it can be used as a weapon of defence and offence.
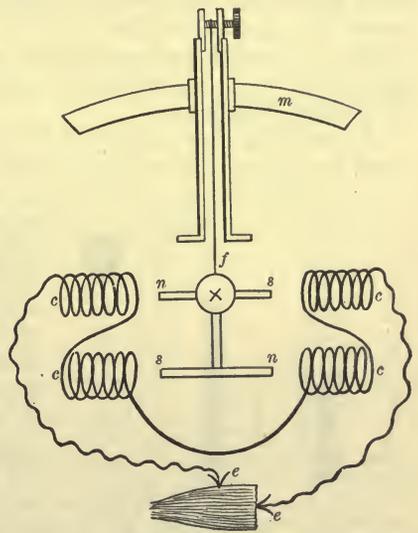
FIG. 58.—Schema of galvanometer: *n, s,* north and south poles of astatic pair of magnets; *m,* compensating magnet, held by friction on the staff, and capable of being approached to, or rotated with reference to, the suspended magnet; ×, mirror; *f,* fibre supporting the magnets; *c, c, c, c,* coils of wire to carry the electric current near to the magnets, the upper coils being wound in the opposite direction to the lower; *e, e,* non-polarizable electrodes applied to the longitudinal surface and cross section of a muscle.

1. **Methods of Ascertaining the Electrical Condition of a Muscle or a Nerve.**—If the electric tension of any two parts of an object differs, the instant they are joined an

electric current will flow from the point where the tension is greater to that where it is less. The presence, direction of flow, and strength of an electric current can be detected by an instrument called a galvanometer. If any two parts of a muscle or nerve, as e, e, Figure 58, be connected by suitable conductors with the coils, c, c, of a galvanometer, and if there be a difference in the electric potential of the two parts examined, an electric current will be indicated by the instrument. In such tests all extra sources of electricity are to be avoided, therefore the electrodes applied to the muscle must be non-polarizable.

The Galvanometer—An ordinary form of galvanometer consists of a magnet suspended by an exceedingly delicate fibre of silk, or quartz, and one or more coils, composed of many windings of pure copper wire, placed vertically near the magnet and in the plane of the magnetic meridian. If an electric current be allowed to flow through the wire, it influences the magnetic field about it, and, if the coils be close to the suspended magnet, causes the magnet to deviate from the plane of the magnetic meridian in one or the other direction, according to the direction of the flow of the current. In the more delicate instruments the influence of the earth's magnetism is lessened by the use of two magnets of as nearly as possible the same strength, placed so as to point in opposite directions, and fastened at the extremities of a light rod. As each magnet tends to point toward the north, they mutually oppose each other, and therefore the effect of the earth's magnetism is partly compensated. Still another magnet may be brought near this "astatic" combination, and by opposing the action of the earth's magnetism make the arrangement even more delicate. In the Thompson galvanometer, the rod connecting the needles bears a slightly concave mirror, from which a beam of light can be reflected on a scale. Or a scale may be placed so that its image falls on the mirror, and the slightest movement of the magnet may be read in the mirror by a telescope.

The galvanometer is very sensitive to the presence of electric currents. Another apparatus which is even more responsive to changes in electric potential of short duration is the capillary electrometer.

The capillary electrometer (Fig. 59) consists of a glass tube (a) drawn out to form a very fine capillary, the end of which dips into a glass cup with parallel sides (f) contain-

ing a 10 per cent. solution of sulphuric acid. The upper part of the tube is connected by a thick-walled rubber tube with a pressure-bulb containing mercury (c). As the pressure-bulb is raised, the mercury is driven into the capillary, the flow being opposed by the capillary resistance. By a sufficiently great pressure, mercury may be driven to the extremity of the capillary and all the air expelled. When the pressure is relieved the mercury rises again in the tube, drawing the sulphuric acid after it. The column of mercury will come to rest at a point where the pressure and the capillary force just balance. Seen through the microscope (e), the end of the column of mercury, where it is in contact with the sulphuric acid appears as a convex meniscus (d). Any alteration of the surface tension of the meniscus causes the mercury to move with great rapidity in one direction or the other along the tube; and a very slight difference of electric potential suffices to cause a change in surface ten-
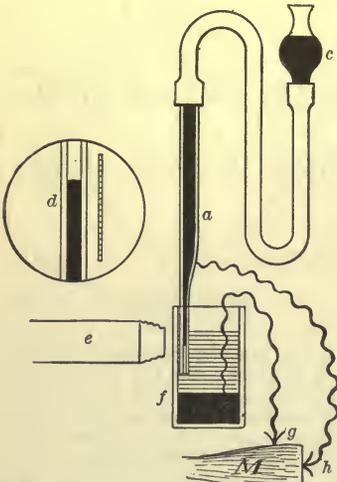
FIG. 59.—Schema of capillary electrometer.

sion of the mercury-sulphuric acid meniscus. A platinum wire fused into the glass tube (a), and another dipped into a little mercury at the bottom of the cup holding the acid, permit the mercury in the capillary and the acid to be connected with the body the electric condition of which is to be examined. If the mercury and acid be connected with two points of different electric potential, as g and h of muscle M, the mercury will instantly

move from the direction of greater to that of lesser tension, descending deeper into the tube if the pressure be raised on the mercury side, or lowered on the acid side, and *vice versa*. As seen through the microscope the picture is reversed (*d*), and the movements of the mercury appear to be in the opposite direction to that stated. The extent of the movements of the mercury column can be estimated by a scale in the eyepiece. Moreover, the movement of the mercury can be recorded photographically, by placing a strong light behind the column of mercury, and letting its shadow fall through a slit in the wall of a dark chamber, upon a sheet of sensitized paper stretched over the surface of a revolving drum or a sensitized plate moved by clockwork or other suitable mechanism. This instrument, of which there are a number of different forms besides that originally devised by Lippmann, is very delicate, recording exceedingly slight differences in electrical potential.

2. **Currents of Rest.**—A normal resting nerve or muscle presents no differences in electric tension and gives no evidence of electric currents, wherefore we say it is iso-electric. If any part of the structure be injured, its electrical condition is forthwith changed, and if the injured portion and some normal part be connected with a galvanometer, an electric current is observed to flow from the normal region to the point of injury. These muscle-currents were discovered at about the same time by Matteucci and Du Bois-Reymond, and the latter wrote a now celebrated treatise upon the electrical phenomena to be observed in the nerve and muscle under varying conditions.[1]

Directions of Currents of Rest.—If a striated muscle, with long parallel fibres, such as the sartorius or the semimembranosus of a frog, be prepared with care not to injure the surface, and then be given a cylindrical shape by cutting off the two ends at right angles to the long axis, the piece will present two cross sections of injured tissue and a normal longitudinal surface (see Fig. 60). If non-polarizable electrodes, connected with the coils of wire of a galvanometer, be applied to various parts of such a piece of muscle, it will be found that all points on the longitudinal surfaces are positive in relation to all points on the cross sections, but that the differences of tension will differ according to the points which are compared. Suppose that the cylinder be divided into equal halves by a plane parallel to the cut ends. Points on the line bounding this plane, the equator, show the

FIG. 60.—Schema to show the direction of currents to be obtained from muscle. The schema represents a cylindrical piece of muscle with normal longitudinal surface (*a, c* and *b, d*), and two artificial cross sections (*a, b* and *c, d*). The position of the equator is shown by line *e*. The unbroken lines connect points of different potential, and the arrows show the direction which the currents would take were these points connected with a galvanometer. The broken lines connect points of equal potential from which no current would be obtained.

greatest positive tension, and the farther other points on the longitudinal surface are from the equator the less their tension. Points on the cross section show a negative tension, and this lessens from the centre to the periphery of

[1] *Untersuchungen über thierische Elektricität*, Berlin, 1849.

the cross section.   Points on the cross section equidistant from the centre, or on the longitudinal surface equidistant from the equator, have the same potential and give no current, while points placed unsymmetrically give a current. Splitting the cylinder by separation of the parallel fibres gives pieces of muscle which show the same electrical peculiarities, and without doubt the same would be true of separate muscle-fibres or pieces of fibres.

Theories as to Cause of Currents of Rest.—Du Bois-Reymond, impressed by the facts which he had ascertained as to the direction of action of the electro-motive forces exhibited by the muscle, tried to explain the difference in electrical tension of the surface and cross section on the supposition that the muscle was composed of electro-motive molecules which presented differences in electric tension similar to those shown by the smallest particles of muscle which it is possible to study experimentally.   Further, he considered these differences in tension, and the consequent electric currents, to exist within the normal muscle—the longitudinal surface and normal cross section, *i. e.* the point where the muscle-fibre joins the tendon, having the same sort of difference in electric potential as the normal longitudinal surface and the artificial cross section.   When the muscle is injured the balance of the electro-motive forces within is lost, and they are revealed.   It is difficult to refute such a theory by experiment, because our instruments only record differences in tension at points on the surface of the muscle to which we can apply the electrodes. We cannot say that there is an absence of electric tension or lack of electric currents within the normal resting muscle; we can only say that there is no direct experimental evidence of the existence of such currents.

Another theory of the electrical phenomena observed in muscle, and one which has found many adherents, was advanced by Hermann.[1]   According to Hermann's view there are no differences in electric potential and no electric currents within the normal muscle; the "current of rest" is a "current of injury," a "demarcation current," *i. e.* it is due to chemical changes occurring in the dying muscle-tissue at the border line between the injured and living muscle-tissue.

Although the greatest differences in potential are observed when many muscle-fibres are injured, as when a cut is made completely through a muscle, injury to any part causes that part to become negative as compared with the rest. Even an injury to a tendon causes a difference in potential.   It is exceedingly difficult, therefore, to expose a muscle without injuring it; but this can be done in the case of the heart ventricle, and Engelmann showed that this gives no current when at rest, although a current is found as soon as any part is hurt, the part becoming immediately negative in relation to other uninjured parts.   In experiments on isolated, long, parallel-fibred muscles, the current which is caused by the injury of one extremity is found to fade away only very gradually (it may last forty-eight hours or more), and this current can be strengthened but little by new injuries.   In the case of the heart-muscle the current caused by cutting off a piece of the ventricle soon disappears, but another cur-

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[1] *Handbuch der Physiologie,* 1879, Bd. i. p. 226.

rent of equal strength is got if a new section be made by cutting off the tissue injured by the first cut. In the case of the long-fibred muscles the death process gradually progresses the length of the injured fibres, while in the case of the heart-muscle, in which the cells are very short, the death processes are limited to the injured cells, and on their death the current disappears; when a new cut is made other cells are injured and again a strong current is obtained.

Dead tissue gives no current; normal resting living tissue gives no current; dying tissue is electrically negative as compared with normal living tissue.

Hering has carried Hermann's view that electrical change is the result of chemical action still further. He considers that the condition of negativity is an evidence of katabolic (breaking-down) chemical processes and that anabolic (building-up) chemical processes are accompanied by a positive electrical change. Like Du Bois-Reymond, he believes that the normal resting muscle may be the seat of electro-motive forces which do not manifest themselves as long as the different parts are in like condition.

Current of Rest of a Nerve.—Nerves like muscles show no electric currents if normal and resting, but give a demarcation current if injured, the dying portion being negative to normal parts, and the direction of the currents is the same as in injured muscle. Gotch and Horsley[1] ascertained the electro-motive force in the nerve of a cat to be 0.01 of a Daniell cell and of an ape only 0.005, while in the spinal nerve-roots of the cat it was 0.025, and in the tracts of the spinal cord of the cat 0.046 and of the ape 0.029. Larger currents are obtained from non-medullated nerves, probably because a non-medullated nerve contains a larger number of axis-cylinders than a medullated nerve of the same size. The current of injury of a nerve lasts only a short time. The death process which is the immediate result of the injury proceeds along the nerve only a short distance, perhaps to the first node of Ranvier, and when it has ceased to advance the current fails; a new injury of the nerve causes another demarcation current as strong as the first.

Hering found that a nerve like a muscle could be excited by its own current, provided the circuit between the longitudinal and fresh cross section of an irritable nerve was rapidly closed.

3. **Currents of Action in Muscle.**—Just as the dying tissue of nerves is electrically negative as compared with normal tissue, so active nerve- and muscle-tissue is electrically negative as compared with resting tissue.

Du Bois-Reymond discovered that if the normal longitudinal surface and injured cut end of a muscle were connected with a galvanometer and the muscle were tetanized, the magnet swung back in the opposite direction to the deflection which it had received from the current of rest. This backward swing of the magnet was not due to a lessening of the current of rest, for if the effect of the current of rest on the galvanometer were compensated for by a battery current of equal strength and of opposite direction, so that the needle stood at 0, and the muscle were then tetanized, there was a deviation of the needle in the opposite direction to that given it by the current of rest. Du Bois-

[1] *Philosophical Transactions*, 1891, B., vol.182, pp. 267–526.

Reymond called this current of action the negative variation current. This negative variation current was found to last as long as the muscle continued in tetanus. On the cessation of the stimulus the current subsided more or less rapidly and the needle returned more or less completely to the position given it by the current of rest before the excitation. The return was rarely complete, and by repeated excitations there was a gradual lessening of the current of rest, the amount varying with the extent of the preceding irritation.

Secondary Tetanus.—Matteucci and Du Bois-Reymond (1842) both discovered the phenomenon which Du Bois-Reymond called secondary tetanus.
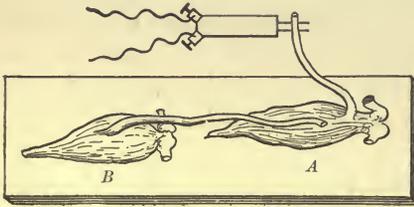
FIG. 61.—Secondary tetanus.

If two nerve-muscle preparations be made, and the nerve of preparation B be laid on the muscle of preparation A, when the nerve of A is stimulated, not only the muscle of A but the muscle of B will twitch (see Fig. 61).

If nerve A be excited by many rapidly following induction shocks so that muscle A enters into tetanus, muscle B will also be tetanized. The phenomenon is not due to a spread of the irritating electric current through nerve and muscle A to nerve B, for the tetanus of both muscles stops if nerve A be ligated; moreover, a secondary tetanus is obtained in case tetanus of muscle A is called out by mechanical stimuli, such as a series of rapid light blows, applied to nerve A.

Du Bois-Reymond considered "secondary tetanus" a proof of the discontinuity of the apparently continuous contraction of tetanus, for muscle B could only have been excited to tetanus by rhythmic excitations from A. Each of the rapidly following excitations applied to A was the cause of a separate contraction process and a separate current of action in B; the separate contractions combined to produce the tetanus of B, but the separate currents of action did not fuse, although they caused a continuous negative variation of the slowly moving magnet of the galvanometer.

The correctness of this view has been shown by experiments with the capillary electrometer, which approaches the "physiological rheoscope," as the nerve-muscle preparation is called, in its sensitiveness to rapid changes in electrical potential.

Burdon Sanderson [1] has obtained, by photographically recording the movements of the column of mercury of the capillary electrometer (see Fig. 59, p. 136), beautiful records of the changes of electric potential which occur when an injured muscle is tetanized.

The record in Figure 62 shows, first, a series of negative changes resulting from the separate stimuli. It is these which cause secondary tetanus and which produced the negative variation current disclosed by the galvanometer in the experiments of Du Bois-Reymond. Second, there is a more permanent negative change, likewise opposed to and lessening the effect of the negative

[1] *Journal of Physiology*, 1895, vol. xviii. p. 717.

change at the part where the tissue is dying, and called by Sanderson "the diminutional effect." This continuous negative change is probably attributable to the presence of a continuous contraction process, perhaps the contracture which we observed in studying the tetanus curve (see Fig. 49). This "diminu-

FIG. 62.—Record of changes in electric potential in a tetanized injured muscle of a frog. The leading-off non-polarizable electrodes connected with the capillary electrometer touched the normal longitudinal and injured cut surface of the muscle. The muscle was tetanized by an induction current applied to its nerve, the rate of interruptions being 210 per second. A rise of the curve indicates an electrical change of opposite direction to that caused by the injury. The diminution of the current of injury, which was less than in some other experiments, was 0.008 volt. The time record at the bottom of the curve was obtained from a tuning fork making 500 double vibrations per second (after Burdon Sanderson).

tional effect" is only to be observed upon an injured muscle, since it represents a difference in potential between the normally contracting and the injured, imperfectly contracting muscle-substance. When all parts of the muscle are normal and contracting to an equal amount, the electrical forces would be everywhere of the same nature, balance one another, and give no external evidence. Although the diminutional effect is only to be observed upon the injured muscle, the temporary negative changes which follow each excitation are to be observed on the normal muscle. To understand this we must consider the diphasic current of action.

Diphasic Current of Action.—If a normal muscle be locally stimulated by a single irritation, either directly or indirectly through its nerve, the part excited will be the first to become active and electrically negative, and this condition will be taken on later by other parts. Our methods only permit us to observe the relative condition of the parts of the muscle to which the electrodes are applied, the changes in the intermediate tissue failing to show themselves. If an electrode be applied near the place where the uninjured muscle is stimulated, *A*, and another at some distant point, *B*, and these electrodes be connected with a capillary electrometer, a diphasic electrical change will be observed to follow each stimulation. At the instant the irritant is applied the muscle-substance at *A* will become suddenly negative with respect to that at *B*; when the spreading irritation-wave has reached *B*, that part too will tend to be negative, and an electrical equality will be temporarily established; finally, *B* continuing to be active after *A* has ceased to act, *B* will be negative in respect to *A*. Since the wave of excitation spreads along the fibres in both directions from the point irritated, each excitation will cause two such diphasic electrical changes.

If the muscle has been injured at B, the dying fibres there will react but poorly to the stimulus, and therefore the antagonistic influence of the negative change at B will incompletely compensate for the negativity at A, and hence only a single phase due to the condition of negativity at A will be seen.

The normally beating heart shows diphasic currents of action : in the first phase the base, where the contraction process starts, is negative to the apex, and in the second phase the apex is negative to the base. In case the heart be injured, the negative change corresponding to action fails at the injured part, and therefore a single and because not antagonized more prolonged negative change is observed. Under certain conditions a triphasic change is observed, which need not be discussed here. Waller[1] has succeeded in recording the electrical changes which accompany the beat of the human heart.

These diphasic changes of the electric condition are sufficiently strong and rapid in the mammalian heart to excite the nerve of a nerve-muscle preparation, and the muscle will be seen to give one, or, if the heart is uninjured, sometimes two, contractions every time the heart beats.

Bernstein[2] found the time between the two portions of diphasic change to be proportional to the distance between the leading-off electrodes, and to correspond to a rate of transmission the same as that of the wave of excitation as revealed by the spread of the contraction process (in the muscle of the frog 3 meters per second). Hermann,[3] by using cord electrodes on the human forearm, found the rate of spread of the active process by the voluntary contraction of human muscle to be from 10 to 13 meters per second. Du Bois-Reymond dipped a finger of each hand into fluid contained in cups connected with a galvanometer. If the muscles of one arm were vigorously contracted, a deflection of the magnet was seen. This was probably due to electric currents from the glands of the skin and not from the contracting muscles. Bernstein found that the negative change began at the instant of excitation, *i. e.* during what was considered the latent period, and hence he thought that it preceded the contraction process and represented the excitation process. It is now believed that the katabolic chemical changes which result in the development of the three forms of energy, heat, motion, and electricity, have little or no latent period, but begin at the instant the irritant acts, being practically synchronous with the excitation process (see p. 101). The condition of negativity is considered not to result from an irritation process preceding the contraction, but to be associated with the contraction process itself, and this view is supported by the discovery that the negative state continues throughout the contraction. Sanderson and Page[4] saw the diphasic change which accompanies the beat of the heart last throughout the contraction.

Lee[5] found the diphasic change which occurs when the skeletal muscle of

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[1] *Archiv für Anatomie und Physiologie*, 1890 ; physiol. Abtheil., p. 187.

[2] *Untersuchungen über den Erregungsvorgang im Nerven- und Muskel-systeme*, 1871.

[3] *Handbuch der Physiologie*, 1879, i. 1, p. 224.

[4] *Journal of Physiology*, 1879, vol. ii., p. 396.

[5] *Archiv für Anatomie und Physiologie*, 1887, p. 204.

a frog is excited by a single stimulus to continue as long as the muscle remains active, including the period relaxation; in some cases it lasted from 0.05 to 0.06 second. Sanderson, as we have seen (see Fig. 62), tetanized injured skeletal muscles of the frog, and found not only a series of negative variations corresponding to the contraction processes which resulted from the separate excitations, but a continuous negative variation, the diminutional effect, which developed comparatively slowly and lasted after the irritant had ceased to act. All these facts unite to point to the conclusion that the negative electrical change which develops when a muscle is excited to action is associated with the contraction process.

4. **Currents of Action in Nerves.**—In general, the facts which have been stated with regard to the current of action in muscles apply to nerves. When a normal nerve is excited a negative change is forthwith developed at the stimulated point and passes thence in both directions along the nerve at the same rate as the nerve impulse. This change is diphasic, first the part excited and later distant parts showing the negative change. If the nerve be injured, and the normal surface be compared with the dying or dead cross section, the second phase is absent. If the nerve be frequently excited, each excitation awakens a separate current of action. The duration of the negative change caused by a single stimulus varies in different conditions from 0.007 to 0.023 second. The strength of the current of action likewise varies, but under favorable conditions may be twice as great as the current of rest,[1] and Hering has shown that it is capable of exciting another nerve to action. Nerve-cells and muscles are more sensitive to nerve impulses than our instruments are to the accompanying electrical changes, nevertheless a negative change may be observed to accompany a nerve impulse which has been caused by the excitation of the nerve by nerve-cells.

Du Bois-Reymond observed with the galvanometer a lessening ("negative variation") of the demarcation current ("current of rest") when in strychnia-poisoning the spinal motor nerve-cells were exciting the motor nerves vigorously and causing cramp-like tetanic muscular contractions. Gotch and Horsley[2] applied electrodes connected with a capillary electrometer to peripheral nerves, spinal nerve-roots, and tracts of motor fibres within the spinal cord, and discovered that if the cortical brain-cells in the motor zones were excited, the nerves showed currents of action corresponding in rate to the discharge of motor impulses from these brain-cells, e. g. if the epileptiform convulsions were occurring at the time, the capillary electrometer revealed changes of potential of like rate in the nerves.

As far as has been ascertained the nerve impulse has the same general characteristics in all forms of nerves, medullated and non-medullated, sensory, inhibitory and motor, and except as regards strength, rhythm, etc. is the same whether they be excited artificially or normally by a nerve-cell or sensory end-organ. In every case the impulse appears to be accompanied by a current of

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[1] Biedermann: *Elektrophysiologie*, 1895, p. 666.
[2] *Philosophical Transactions*, 1891, vol. 182, pp. 267–526.

action, *e. g.* light falling on the retina of the eye of a frog causes a negative variation of the current of rest of the optic nerve.

F. Chemistry of Muscle and Nerve.

I. Chemistry of Muscle.

Muscles contain about 75 parts water and 25 parts solids; nearly 21 parts of the solids are proteids, the remaining 4 parts consisting of fats, extractives, and salts.

Little is known concerning the chemistry of living muscle; the instability of the complex molecules which makes possible the rapid development of energy peculiar to muscles renders exact analysis impossible. The manipulations essential to chemical analysis necessarily alter and kill the muscle protoplasm.

Death of the muscle is ordinarily associated with a peculiar chemical change known as *rigor mortis.* To understand the chemical composition of muscle it is necessary that we should consider the nature of this change.

1. **Rigor Mortis.**—*Rigor mortis,* the rigidity of death, is the result of a chemical change in the substance of a muscle by which it is permanently altered, its irritability and other vital properties being irretrievably lost. The change is manifested by a loss of translucency, the muscle becoming opaque, and by a gradual contraction, accompanied by a development of heat and acidity, and resulting in the muscle being stiff and firm to the touch, less elastic, and less extensible. Whenever muscle dies it undergoes this change.

Conditions which Influence the Development of Rigor.—Ordinarily on the death of the body the muscle enters into rigor slowly—the muscle-fibres are involved one after the other, and through the gradual contraction and hardening of the antagonistic muscles the joints become fixed and the body acquires the rigidity which we associate with death. Rigor usually affects the different parts of the body in a regular order, from above downward, the jaw, neck, trunk, arms, and legs being influenced one after the other. The position taken by the body is generally determined by the weight of the parts and the relative strength of the contractions of the muscles.

The time required for the appearance of rigor is very variable. It is determined in part by the nature of the muscle, its condition at the moment of death, and the temperature to which it is subjected. The muscles of warm-blooded animals enter into rigor more quickly than those of cold-blooded animals; of the warm-blooded animals, pale muscles more quickly than red, and the flexors before the extensors; of the cold-blooded animals, frog's muscles more quickly than those of the turtle. In general, the more active the muscle protoplasm, the more rapid are the chemical changes which it undergoes, and amongst these the coagulation of rigor mortis.

The condition of the muscle plays a very important part in determining the onset of rigor. If the muscles are strong and vigorous and death of the body has come suddenly, rigor develops slowly; if the muscles have been enfeebled by disease or fatigued by great exertion shortly before death, it comes rapidly.

In the case of wasting diseases rigor comes quickly, is poorly developed, and passes off quickly; when the muscles are fatigued at the time of death, as in the case of a hunted animal, it comes quickly. We hear of soldiers found dead on the field of battle grasping the sword, as if the muscular contractions of life had been continued by the contractions of death. In the case of certain diseases of the spinal cord and brain, too, rigor may come so rapidly that the limbs may maintain the position which they had at the time of death, "cataleptic rigor," as it has been called. The coming on of rigor is particularly striking in the case of diseases which, like cholera, are accompanied by violent muscular cramps and lead to a rapid death. It is not uncommon, in such cases, for the contractions of rigor to cause movements which may mislead a watcher into supposing the dead man to be still alive. This idea is favored by the fact that the body may remain warm, owing to the heat which is produced in the muscles as a result of the chemical changes occurring during rigor. The post-mortem muscular contractions and the rise of temperature observed in such cases are only excessive manifestations of what always occurs on the death of the muscle. The movements are probably due, in part, to the rapidity with which the muscles contract in rigor, and in part to the fact that the antagonistic muscles are not affected at the same time to the same degree. Whether the contractions are partly excited by changes accompanying the death of the motor nerve-cells in the central nervous system is uncertain, but not impossible. Muscles are still able to respond by contractions to stimuli coming to them through the nerve, even after rigor has become quite pronounced, probably because the coagulation process attacks the different fibres at different rates, and certain of the fibres are still alive and irritable after the others are dead and coagulated.

Many observers favor the view that the central nervous system influences muscles after the death of the body as a whole, and by weak stimuli resulting from the changes in the nerve-cells excites chemical changes in the muscles which favor the coming on of rigor.[1] In proof of this it is stated that curarized muscles enter into rigor more slowly than non-curarized. Undoubtedly stimulation of the nerve, or, indeed, anything which would excite a muscle to action, tends to put it in a condition favorable to the coming on of rigor; whether the influence exerted by the central nervous system is more than this is very questionable.

Temperature has a marked influence on the development of rigor mortis. Cold delays and warmth favors, 38°–40° C. being most favorable. Since rigor is the result of a chemical change, these effects of temperature are what one would have expected. Other forms of chemical change which are attributable to ferment action are found to be the most vigorous at a temperature of about 40° C.

In general, it may be said that rigor in warm-blooded animals comes on in from ten minutes to seven hours after death, although some state that it may come as late as eighteen hours. It lasts anywhere from one to six days.

[1] Brown-Séquard: *Archives de Physiologie*, 1889, p. 675.

The sooner it comes on, the sooner it goes off. The stiffness can be broken up artificially by forced movements of the parts, and when thus destroyed does not return, provided the rigor was complete at the time.

The Cause and Nature of the Contraction of Rigor Mortis.—The most likely explanation of the contraction of the dying muscle is that it is the result of the coagulation of a part of the semi-fluid muscle-substance within the sarcolemma. This was suggested by Bruecke, and Kuehne proved that such a coagulation change takes place, by showing that the semi-fluid muscle-substance, "the muscle-plasma," if expressed from the frozen muscle, coagulates on being warmed. The coagulation is a chemical change attributed to the action of a ferment, the myosin ferment, which is thought to be formed at the death of the muscle.

Another, though less generally accepted view, is that the contraction of the muscle seen in rigor is of the same nature as ordinary muscular contractions.[1] Prolonged muscle contractions are observed when a muscle is greatly fatigued or subjected to such a drug as veratria (see p. 128), and there are many points of resemblance between the contraction of normal and dying muscle—viz. the change of form, the production of heat, the formation of sarcolactic acid, the using up of oxygen and the production of carbon dioxide, and the fact that the dying and presumably coagulating muscle is, like normal contracting muscle, electrically negative as compared with normal resting muscle. To this may be added that, as has been said, the muscle continues to be irritable even when rigor is quite advanced, and that it enters into rigor more quickly if left in connection with the central nervous system.

On the other hand, one cannot fail to be impressed with the differences between the two forms of contraction.

Normal Contracting Muscle.	*Muscle contracting by Rigor Mortis.*
Contains uncoagulated myosinogen.	Contains coagulated myosin.
Is translucent.	Is opaque.
Is soft and flexible.	Is firm and stiff.
Is no less elastic than in repose.	Is less elastic than before.
Is more extensible than in repose.	Is less extensible than before.
Contracts rapidly.	Contracts very slowly, as a rule.
Fatigues rapidly and relaxes.	Remains contracted a long time.

Furthermore, it may be added that normal contractions only occur when the irritable muscle is stimulated, while a muscle can enter into rigor when its irritability has been taken away by subjecting it to oxalate solutions,[2] also, when it has been curarized and so shut out from all nervous influences.[3]

Rigor is not confined to the voluntary muscles, though it is less easily observed in the case of most involuntary muscles. The heart enters rapidly into rigor, with the formation of sarcolactic acid. The non-striated muscle of the stomach and ureters, too, has been seen to undergo this change.

[1] Hermann: *Handbuch der Physiologie*, 1879, Bd. i. p 146.
[2] Howell: *Journal of Physiology*, 1893, vol. xiv. p. 476.
[3] Nagel: *Pflüger's Archiv*, vol. lviii. S. 279.

The passing off of rigor mortis is usually accompanied by beginning decomposition, and, indeed, it is generally supposed that the decomposition is the cause of softening of the muscle. This is denied by certain observers, and it is stated that rigor may pass off when the presence of putrefactive organisms is excluded by special aseptic precautions.

The Chemical Changes which accompany the Development of Rigor.—Rigor mortis is characterized by the coagulation of a part of the muscle-substance; this can be prevented by a temperature a little below 0° C. Cold, although temporarily depriving the muscle of its irritability, does not, unless extreme and long-continued, kill the muscle protoplasm. Frogs can be frozen stiff and recover their activity when they thaw out. Indeed, this probably happens not infrequently to the frogs hibernating in holes in the banks of ponds. Since cold prevents coagulation without destroying the life of the muscle protoplasm, we can by its aid isolate the living muscle-substance from the nerves, blood-vessels, connective tissue, and sarcolemma of the muscle, but as soon as we begin to analyze it it loses its living structure. This method of obtaining muscle-plasma was introduced by Kuehne[1] in the study of the muscles of frogs, and was later employed with slight modifications by Halliburton[2] for the muscles of warm-blooded animals. The blood was washed out of the vessels with a stream of 0.6 per cent. sodium-chloride solution at 5° C.; the irritable muscles were then quickly cut out and frozen in a mixture of ice and salt at 12° C. The frozen muscle was then cut up finely in the cold, and a yellowish, somewhat viscid, and faintly alkaline muscle-plasma was squeezed out. This fluid was found to coagulate in twenty to thirty minutes at a temperature of 40° C.; if the temperature were lower the coagulation was slower. The clot, which was jelly-like and translucent, contracted slowly and in a few hours squeezed out a few drops of serum. The coagulated material formed in the clot is called myosin. It dissolves readily in dilute neutral saline solutions, as a 10 per cent. solution of sodium chloride or a 5 per cent. solution of magnesium sulphate, and its saline solutions are precipitated in an excess of water or by saturation with sodium chloride, magnesium sulphate, or ammonium sulphate; it has, in short, the characteristics of a globulin. Chittenden and Cummins state that it has the following composition: C 52.82, H 7.11, N 16.17, S 1.27, O 22.03.

Halliburton, in studying the coagulation of muscle, followed for the sake of comparison the methods which have been employed in the study of coagulation of blood. He found that muscle-plasma, like blood-plasma, is prevented from coagulating not only by cold, but by neutral salts, such as magnesium sulphate, sodium chloride, and sodium sulphate; and further, that the salted plasma if diluted coagulates.

The points of resemblance between the coagulation of myosin and fibrin suggest a similar cause, and Halliburton succeeded in obtaining from muscles coagulated by long standing in alcohol a watery extract, which greatly hastened

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[1] *Untersuchungen über das Protoplasma*, Leipzig, 1864.
[2] *Journal of Physiology*, 1887, vol. viii. p. 134.

the coagulation of muscle-plasma and myosin solutions. He called the substance thus obtained myosin ferment. The extract obtained contained an albumose which was either the ferment or held it in close combination. The pure ferment has not been isolated. The myosin ferment is not the same as fibrin ferment, since neither can do the work of the other. Moreover, fibrin ferment is destroyed at 75°–80° C. and myosin ferment is not destroyed till 100° C.

In several respects there is a close resemblance between the behavior of blood- and muscle-plasma, but the coagulated products differ. Kuehne found that myosin could be dissolved by a dilute saline solution, and that, on further dilution, it was reprecipitated. Halliburton observed that a saline solution of myosin, diluted twenty times with water, gave a precipitate which could be dissolved in a 5 per cent. magnesium-sulphate solution, and then by the addition of water be made to recoagulate. In these respects myosin differs markedly from fibrin. Fibrin is dissolved only with difficulty in dilute saline solutions and cannot be recoagulated. Myosin also differs from fibrin by its greater solubility in dilute HCl.

Moreover, the chemical change which results in the formation of myosin is different from that which produces fibrin. The clotting of muscle-plasma and the formation of myosin is accompanied or closely followed by the production of an acid, while no such change occurs during the coagulation of blood-plasma. In the earlier stages of clotting the acidity may be due in part to acid potassium phosphate, but the final acidity is chiefly due to lactic acid. The source of the lactic acid has not been definitely made out. The view that it comes from glycogen is made questionable by Boehm's[1] observation that the amount of glycogen is not lessened in rigor, and is corroborated by the observation that the muscles of starving animals become acid when entering into rigor, although, as Bernard found, they contain no glycogen. Boehme concluded that the sarcolactic acid is formed from the proteids, and this is accepted by other good observers.

Some writers have thought the coagulation of the muscle was the result of the formation of an acid by the dying muscle. This is unlikely, although the presence of acid, like that of many other substances, quinine, caffein, digitalin, veratrin, hydrocyanic acid, ether, chloroform, etc.,[2] may hasten the process. This may account for the rapidity with which rigor comes on in fatigued muscles.

2. **Constituents of Muscle-serum and Changes resulting from Contraction.**—Muscle-serum can be most readily obtained by mincing a muscle in rigor mortis and expressing the fluid. The proteids of the serum can be separated by the degrees at which they undergo heat-coagulation.

The method of fractional heat-coagulation was employed by Halliburton[3] to determine the proteids of muscle. He found the following:

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[1] *Pflüger's Archiv*, 1880, Bd. xxiii. S. 44.   [2] Halliburton : *Physiological Chemistry*, p. 414.
[3] *Journal of Physiology*, viii. pp. 184–186.

Name.		Temperature of coagulation.
Proteids obtained from the dissolved clot	Paramyosinogen	47° C
	Myosinogen	56° C.
Proteids obtained from muscle-serum	Myoglobulin	63° C.
	Myo-albumin	73° C.
	Myo-albumose	(not coagulated by heat).

The proteids of the serum can also be distinguished by their solubilities in neutral salt-solutions of various strengths. The myoglobulin resembles serum-globulin, although precipitated at 63° C. instead of 73° C. The myo-albumin is apparently identical with serum-albumin.

To these proteids we must add the pigment hæmoglobin. Another pigment, myohæmatin, is also found. It is not unlikely that these pigments have here as elsewhere a respiratory function.

Nitrogenous Extractives.—The chief nitrogenous extractive is creatin; in addition to this we find small amounts of creatinin and of various xanthin bodies, as xanthin, hypoxanthin, carnin, and sometimes traces of urea, uric acid, taurin, and glycocoll. The chemical nature of these bodies need not be considered here. Physiologically they may be regarded as waste products which result from the partial oxidation of the proteids of muscle during the katabolic processes which are continually occurring even in the resting muscle protoplasm. Monari has shown that the amount of creatin and creatinin is increased by the wear and tear of muscular work, although the proteids of the well-fed muscle probably supply but little of the energy which is set free.[1]

The non-nitrogenous constituents of muscle are fats, glycogen, inosit, sugar, and lactic acid.

Fats are usually found in intermuscular connective tissue, but there is little within the normal fibre. It is doubtful whether fat plays any direct part in the ordinary metabolic processes involved in the action of muscles, although it is probable that if more available sources of energy are lacking it may, like the proteids, be altered and employed. Under pathological conditions large amounts of fat may be found inside the sarcolemma; in phosphorus-poisoning the degenerated muscle protoplasm may be replaced by fat in the form of fine globules.

Glycogen is found in very variable amounts in different muscles. The work of many observers has shown that it is here, as in the liver, a store of carbo-hydrate material, and is employed by the muscle, either directly or after con-version into some other body, as a source of energy. The quantity, which is rarely more than $\frac{1}{2}$ per cent., lessens rapidly during muscle work.

Sugar is found in muscles in small quantities only, nevertheless it probably plays an important part, for Chauveau and Kaufmann, by studying the levator labii superioris of the horse, found that the muscles take sugar from the blood, and that they take more during action than rest. The sugar which the mus-

[1] Fick und Wislicenus: *Vierteljahresschrift der Züricher Naturforschenden Gesellschaft*, 1865, Bd. x. p. 317; Pettenkofer und Voit: *Zeitschrift für Biologie*, 1866, ii.; Voit: *Ibid.*, 1876, vi. S. 305.

cle takes during rest is for the most part stored as glycogen.[1]   Although sugar
is considered a source of muscle-energy, the exact way in which it is employed
is doubtful.

Inorganic Constituents of Muscle.—Amongst the bases, potassium has the
greatest prominence, and sodium next ; magnesium, calcium, and small amounts
of iron are also found.   Of the acids, phosphoric is present in the largest quan-
tities.

Gases of Muscle.—No free oxygen can be extracted, but carbon dioxide
may be obtained, in part free and in part in combination.   A little nitrogen
can also be extracted.   The amount of carbonic acid varies greatly with the con-
dition of the muscle ; for instance, it is much increased by muscle work.   Mus-
cles take up oxygen from the blood freely, especially when active, and
when removed from the body may absorb small amounts from the air.
More oxygen is taken up by the muscle during rest than is liberated as
carbon dioxide, but during action the reverse is the case.[2]   Oxygen is not
retained as free oxygen, but is stored in some combination more stable than
oxyhæmoglobin.   It is by virtue of the combined oxygen that the muscle is
enabled to do its work, but the process is not one of simple oxidation.   That
muscles hold oxygen in available combinations was shown by Hermann, who
ascertained that a muscle can contract hundreds of times in an atmosphere
free from oxygen, and produce water and carbon dioxide.

II. Chemistry of Nerves.

Most of our ideas concerning the chemistry of nerves are based on analysis
of the white and gray matter of the central nervous system.   The white matter
is largely made up of fibres and supporting tissue and the gray matter of nerve-
cells.   The peripheral nerve-fibres are simply a continuation of the structures
in the central nervous system ; the active part of the fibre, the axis-cylinder, is
an outgrowth of the cytoplasm of a nerve-cell, and the surrounding medullary
sheath a continuation of the material which sheaths the axis-cylinder while in
the brain and cord.   It is probable, therefore, that the chemistry of the axis-
cylinder approaches to that of the nerve-cell of which it is a branch, and the
chemistry of the medullary substance is the same outside as inside the central
nervous system.

The white matter of the brain of the ox, which is largely made up of nerve-
fibres, is composed of about 70 parts water and 30 parts solids, about one-half
the latter being cholesterin, about a quarter proteids and connective-tissue sub-
stance, and about a quarter complex fatty bodies, neuro-keratin, salts, chiefly
potassium salts and phosphates, and traces of xanthin, hypoxanthin, etc.

The nerve-fibre has a delicate sheath, the neurilemma, the exact constitution

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[1] *Comptes rendus de la Société de Biologie,* 1886, civ.

[2] Ludwig und Sczelkow : *Sitzungsberichte den k. Akad. Wien,* 1862, Bd. xlv. Abthl. 1 ; and
Ludwig und Schmidt : *Sitzungsberichte den math.-phys. Classe d. k. Sächs. Gesellschaft der Wissen-
schaft.* 1868, Bd. xx. ; Regnault and Reiset : *Annales de Chimie et de Physique,* 1849, 3 me sér.,
xxvi. ; Pflüger : *Pflüger's Archiv,* 1872, vi. ; and others.

of which is unknown, but which is supposed to resemble the sarcolemma and to be composed of a substance similar to elastin. The fibres are bound together by *connective tissue* which on boiling gives gelatin. Within the neurilemma is the *medullary sheath*, which is composed of two elements—viz. (1) neuro-keratin, a material similar to the horny substance of epithelial structures, which forms a sort of loose trellis, or network, and probably acts as a supporting framework to the fibre; (2) a white, highly refracting, semi-fluid material, which fills the meshes of the neuro-keratin network, and which is composed largely of protagon and cholesterin combined with fatty bodies. Protagon is a complex phosphorized nitrogenous compound, which many observers believe to contain lecithin and cerebrin. Both lecithin and cerebrin are fatty bodies possessing nitrogen, and the former phosphorus. These and some other complex fatty bodies probably exist in addition to protagon in the medullary subtance. The formation of the "myelin forms" seen in the medulla of dead nerves is attributed to lecithin. The *axis-cylinder* probably contains most of the proteids of the fibre, chiefly globulins, mixed with complex fatty bodies.

The reaction of the normal living fibre is neutral or slightly alkaline. It is said to become acid after death, but this change is not known to accompany functional activity. Indeed, nothing is known of the physiological import of the chemical constituents of the nerve-fibre or of the chemical changes which occur in the axis-cylinder when it develops or transmits the nerve impulse. The peculiar chemical composition of the medullary substance would suggest that it has a more important function than simply to protect the axis-cylinder. Some have attributed to it nutritive powers, and others have supposed it helped to insulate: it is certain that the axis-cylinder can develop and transmit the nerve impulse without the aid of the medullary sheath, for there is a large class of important nerves—the non-medullated nerves—in which it is lacking.

III. SECRETION.

A. General Considerations.

THE term secretion is meant ordinarily to apply to the liquid or semi-liquid products formed by glandular organs. On careful consideration it becomes evident that the term gland itself is widely applied to a variety of structures differing greatly in their anatomical organization—so much so, in fact, that a general definition of the term covering all cases becomes very indefinite, and as a consequence the conception of what is meant by a secretion becomes correspondingly extended.

Considered from the most general standpoint we might define a gland as a structure composed of one or more gland-cells, epithelial in character, which forms a product, the secretion, which is discharged either upon a free epithelial surface such as the skin or mucous membrane, or upon the closed epithelial surface of the blood- and lymph-cavities. In the former case—that is, when the secretion appears upon a free epithelial surface communicating with the exterior, the product forms what is ordinarily known as a secretion; for the sake of contrast it might be called an external secretion. In the latter case the secretion according to modern nomenclature is designated as an internal secretion. The best-known organs furnishing internal secretions are the liver, the thyroid, and the pancreas. It remains possible, however, that any organ, even those not possessing an epithelial structure, such as the muscles, may give off substances to the blood comparable to the internal secretions—a possibility which indicates how indefinite the distinction between the processes of secretion and of general cell-metabolism may become if the analysis is carried sufficiently far. If we consider only the external secretions definition and generalization become much easier, for in these cases the secreting surface is always an epithelial structure which, when it possesses a certain organization, is designated as a gland. The type upon which these secreting surfaces are constructed is illustrated in Figure 63. The type consists of an

FIG. 63.—Plan of a secreting membrane.

epithelium placed upon a basement membrane, while upon the other side of the membrane are blood-capillaries and lymph-spaces. The secretion is derived ultimately from the blood and is discharged upon the free epithelial surface, which is supposed to communicate with the exterior. The mucous membrane of the alimentary canal from stomach to rectum may be considered,

if we neglect the existence of the villi and crypts, as representing a secreting surface constructed on this type. If we suppose such a membrane to become
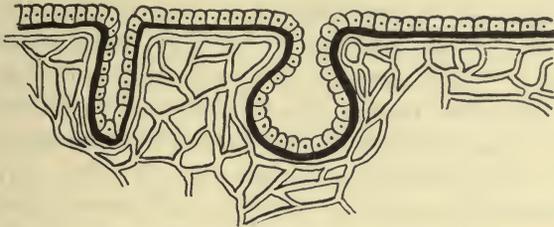
Fig. 64.—To illustrate the simplest form of a tubular and a racemose or acinous gland.

invaginated to form a tube or a sac possessing a definite lumen (see Fig. 64), we have then what may be designated technically as a gland.

It is obvious that in this case the gland may be a simple pouch, tubular or saccular in shape (Fig. 65), or it may attain a varying degree of complexity by the elongation of the involuted portion and the development of side branches
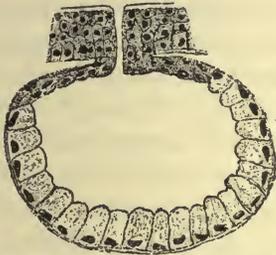
Fig. 65.—Simple alveolar gland of the amphibian skin (after Flemming).
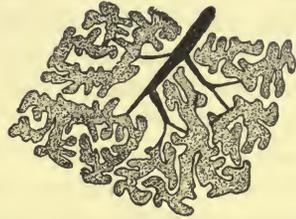
Fig. 66.—Schematic representation of a lobe of a compound tubular gland (after Flemming).

(Fig. 66). The more complex structures of this character are known sometimes as compound glands, and are further described as tubular, or racemose (saccular), or tubulo-racemose, according as the terminations of the invaginations are tubular, or saccular, or intermediate in shape.[1] As a matter of fact we find the greatest variety in the structure of the glands imbedded in the cutaneous and mucous surfaces, a variety extending from the simplest form of crypts or tubes to very complicated organs possessing an anatomical independence and definite vascular and nerve-supplies as in the case of the salivary glands or the kidney. In compound glands it is generally assumed that the terminal portions of the tubes alone form the secretions, and these are designated as the the acini or alveoli, while the tubes connecting the alveoli with the exterior are known as the ducts, and it is supposed that their lining epithelium is devoid of secretory activity.

The secretions formed by these glands are as varied in composition as the glands are in structure. If we neglect the case of the so-called reproductive

[1] Flemming has called attention to the fact that most of the so-called compound racemose glands, salivary glands, pancreas, etc., do not contain terminal sacs or acini at the ends of the system of ducts; on the contrary, the final secreting portions are cylindrical tubes, and such glands are better designated as compound tubular glands.

glands, the ovary and testis, whose right to the designation of glands is doubtful, we may say that the secretions in the mammalian body are liquid or semiliquid in character and are composed of water, inorganic salts, and various organic compounds. With regard to the last-mentioned constituent the secretions differ greatly. In some cases the organic substances present are not found in the blood, and furthermore they may be specific to a particular secretion, so that we must suppose that these constituents at least are constructed in the gland itself. In other cases the organic elements may be present in the blood, and are merely eliminated from it by the gland, as in the case of the urea found in the urine. Johannes Müller long ago made this distinction, and spoke of secretions of the latter kind as excretions, a term which we still use and which carries to our minds also the implication that the substances so named are waste products whose retention would be injurious to the economy. Excretion as above defined is not a term, however, which is capable of exact application to any secretion as a whole. Urine, for example, contains some constituents which are probably formed within the kidney itself, *e. g.* hippuric acid; while, on the other hand, in most secretions the water and inorganic salts are derived directly from the blood or lymph. So, too, some secretions—for example, the bile—carry off waste products which may be regarded as mere excretions, and at the same time contain constituents (the bile salts) which are of immediate value to the whole organism. Excretion is therefore a name which we may apply conveniently to the process of removal of waste products from the body, or to particular constituents of certain secretions, but no fundamental distinction can be made between the method of their elimination and that of the formation of secreted products in general. Owing to the diversity in composition of the various external secretions and the obvious difference in the extent to which the glandular epithelium participates in the process in different glands, a general theory of secretion cannot be formulated. The kinds of activity seem to be as varied as is the metabolism of the tissues in general.

It was formerly believed that the formation of the secretions was dependent mainly if not entirely upon the physical processes of filtration, imbibition, and diffusion. The basement membrane with its lining epithelium was supposed to constitute a membrane through which various products of the blood or lymph passed by filtration and diffusion, and the variation in composition of the secretions was referred to differences in structure and chemical properties of the dialyzing membrane. The significant point about this view is that the epithelial cells were supposed to play a passive part in the process; the metabolic processes within the cytoplasm of the cells were not believed to affect the composition of the secreted product. As compared with this view the striking peculiarity of modern ideas of secretion is, perhaps, the importance attributed to the living structure and properties of the epithelial cells. It is believed generally now that the glandular epithelium takes a direct part in the production of some if not all of the constituents of the secretions. The reasons for this view will be brought out in detail further on in describing the secreting processes of the separate glands. Some of the general facts, how-

ever, which influenced physiologists in coming to this conclusion are as follows :

Microscopic examination has demonstrated clearly that in many cases parts of the epithelial cell-substance can be followed into the secretion. In the sebaceous secretion the cells seem to break down completely to form the material of the secretion ; in the formation of mucus by the goblet cells of the mucous membrane of the stomach and intestines a portion of the cytoplasm after undergoing a mucoid degeneration is extruded bodily from the cell to form the secretion ; in the mammary glands a portion of the substance of the epithelial cells is likewise broken off and disintegrated in the act of secretion, while in other glands the material of the secretion is deposited within the cell in the form of visible granules which during the act of secretion may be observed to disappear, apparently by dissolution in the stream of water passing through the cell. Facts like these show that some at least of the products of secretion arise from the substance of the gland-cells, and may be considered as representing the results of a metabolism within the cell-substance. From this standpoint, therefore, we may explain the variations in the organic constituents of the secretions by referring them to the different kinds of metabolism existing in the different gland-cells. The existence of distinct secretory nerves to many of the glands is also a fact favoring the view of an active participation of the gland-cells in the formation of the secretion. The first discovery of this class of nerve-fibres we owe to Ludwig, who (in 1851) showed that stimulation of the chorda tympani nerve causes a strong secretion from the submaxillary gland. Later investigations have demonstrated the existence of similar nerve-fibres to many other glands—for example, the lachrymal glands, the sweat-glands, the gastric glands, the pancreas. It is asserted also that, in some cases at least, the increased secretion is accompanied by an elevation in temperature of the gland, which speaks for an increased metabolic activity. Moreover, there is considerable evidence, which will be given in the proper place, to show that the secretory fibres are of two kinds, one controlling the production of the organic elements, and one increasing the flow of water and inorganic salts. Recent microscopic work indicates that the secretory fibres end in a fine plexus between and round the epithelial cells, and we may infer from this that the action of the nerve-impulses conducted by these fibres is exerted directly upon the gland-cells.

The formation of the water and inorganic salts present in the various secretions offers a problem the general nature of which may be referred to appropriately in this connection, although detailed statements must be reserved until the several secretions are specially described. The problem involves, indeed, not only the well-recognized secretions, but also the lymph itself as well as the various normal and pathological exudations. Formerly the occurrence of these substances was explained by the action of the physical processes of filtration and diffusion through membranes. With the blood under a considerable pressure and with a certain concentration in salts on one side of the basement membrane, and on the other a liquid under low pressure and differ-

ing in chemical composition, it would seem inevitable that water should filter through the membrane and that processes of osmosis would be set up, further changing the nature of the secretion. Upon this theory the water and salts in all secretions were regarded merely as transudatory products, and so far as they were concerned the epithelium was supposed to act simply as a dead membrane. This theory has not proved entirely acceptable for various reasons. It has been shown that living membranes offer considerable resistance to filtration even when the liquid pressure on one side is much greater than on the other. Tigerstedt[1] and Santessen, for instance, found that a lung taken from a frog just killed gave no filtrate when its cavity was distended by liquid under a pressure of 18 to 20 centimeters, provided the liquid used was one that did not injure the tissue. If, however, the lung-tissue was killed by heat or otherwise, filtration occurred readily under the same pressure. In some glands, also, the formation of the water and salts, as has been said, is obviously under the control of nerve-fibres, and this fact is difficult to reconcile with the idea that the epithelial cells are merely passive filters. In glands like the kidney, and in other glands as well, it has been shown that the amount of water and salts does not increase in proportion to the rise of blood-pressure within the capillaries, as should happen if filtration were the sole agent at work, and furthermore, certain chemical substances when injected into the blood may increase the flow of water in the secretion to an extent that cannot be well accounted for in any other way than by supposing that they act as chemical stimuli to the epithelial cells.

While, therefore, it cannot be denied that the anatomical conditions prevailing in the glands are favorable to the processes of filtration and osmosis, and while no one is justified in denying that these processes do actually occur and seem to account in part for the appearance of the water and inorganic salts, it seems to be clear that in the present condition of our knowledge these factors alone do not suffice to explain all the phenomena connected with the secretion of water and salts. We must suppose that the epithelial cells are actively concerned in the process. The way in which they act is not known ; various hypotheses have been advanced, but none of them meets all the facts to be explained, and at present it is customary to refer the matter to the vital properties of the cells—that is, to the peculiar physical or chemical properties connected with their living structure.

We may now pass to a consideration of the facts known with regard to the physiology of the different glands considered merely as secretory organs. The functional value of the secretions will be found described in the sections on Digestion and Nutrition.

B. MUCOUS AND ALBUMINOUS (SEROUS) TYPES OF GLANDS ; SALIVARY GLANDS.

Mucous and Albuminous Glands.—Heidenhain recognized two types reasons for the mucous and the albuminous, basing his distinction upon the secreting proce: *vom physiol. Lab. des Carol. med.-chir. Instituts in Stockholm,* 1885.

character of the secretion and upon the histological appearance of the secreting cells. The classification as originally made was applied only to the salivary glands and to similar glands found in the mucous membranes of the mouth and œsophagus, the air-passages, conjunctiva, etc. The chemical difference in the secretions of the two types consists in the fact that the secretion of the albuminous (or serous) glands is thin and watery, containing in addition to possible enzymes only water, inorganic salts, and small quantities of albumin; while that of the mucous glands is stringy and viscid owing to the presence of mucin. As examples of the albuminous glands we have the parotid in man and the mammalia generally, the submaxillary in some animals (rabbit), some of the glands of the mucous membrane of the mouth and nasal cavities, and the lachrymal glands. As examples of the mucous glands, the submaxillary in man and most mammals, the sublingual, the orbital, and some of the glands of the mucous membrane of the mouth-cavity, œsophagus, and air-passages. The histological appearance of the secretory cells in the albuminous glands is in typical cases markedly different from that of the cells in the mucous glands. In the albuminous glands the cells are small and densely filled with granular material, so that the cell outlines, in preparations from the fresh gland, cannot be distinguished (see Figs. 70 and 72). In the mucous glands, on the contrary, the cells are larger and much clearer (see Fig. 73). In microscopic preparations of the fresh gland the cells, to use Langley's expression, present the appearance of ground glass, and granules are only indistinctly seen. Treatment with proper reagents brings out the granules, which are, however, larger and less densely packed than in the albuminous glands, and are imbedded in a clear homogeneous substance. Histological examination shows, moreover, that in some glands, *e. g.* the submaxillary gland, cells of both types occur. Such a gland is usually spoken of as a mucous gland, since its secretion contains mucin, but histologically it is a mixed gland. The terms mucous and albuminous or serous, as applied to the entire gland, are not in fact perfectly satisfactory, since not only do the mucous glands usually contain some secretory cells of the albuminous type, but albuminous glands, such as the parotid, may also contain cells belonging to the mucous type. The distinction is more satisfactory when it is applied to the individual cells, since the formation of mucin within a secreting cell seems to present a definite histological picture, and we can recognize microscopically a mucous cell from an albuminous cell although the two may occur together in a single alveolus.

Goblet Cells.—The goblet cells found in the epithelium of the intestine afford an interesting example of mucous cells. The epithelium of the intestine is a simple columnar epithelium. Scattered among the columnar cells are found cells containing mucin. These cells are originally columnar in shape like the neighboring cells, but their protoplasm undergoes a chemical change of such a character that mucin is produced, causing the cell to become swollen at its free extremity, whence the name of goblet cell. It has been shown that the mucin is formed with the substance of the protoplasm as distinct granules

of a large size, and that the amount of mucin increases gradually, forcing the nucleus and a small part of the unchanged protoplasm toward the base of the cell. Eventually the mucin is extruded bodily into the lumen of the intestine, leaving behind a partially empty cell with the nucleus and a small remnant of protoplasm (see Fig. 67). The complete life-history of these cells is imper-
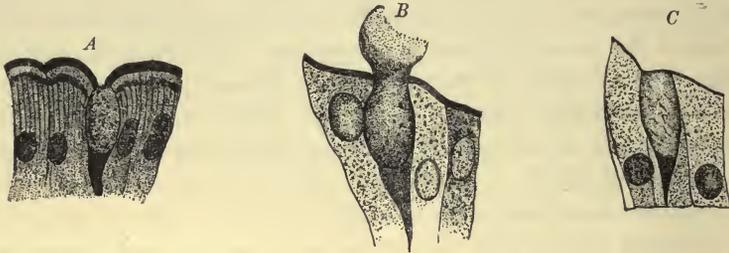
FIG. 67.—Formation of secretion of mucus in the goblet cells: A, cell containing mucin; B, escape of the mucin; C, after escape of the mucin (after Paneth).

fectly known. According to Bizzozero[1] they are a distinct variety of cell and are not genetically related to the ordinary granular epithelial cells by which they are surrounded. According to others, any of the columnar epithelial cells may become a goblet cell by the formation of mucin within its interior, and after the mucin is extruded the cell regenerates its protoplasm and becomes again an ordinary epithelial cell. However this may be, the interesting fact from a physiological standpoint is that these goblet cells are genuine unicellular mucous glands; moreover, the deposition of the mucin in the form of definite granules within the protoplasm gives histological proof that this material is produced by a metabolism of the cell-substance itself. It will be found that the mucin cells in the secreting tubules of the salivary glands exhibit similar appearances. So far as is known, the goblet cells do not possess secretory nerves.

SALIVARY GLANDS.

Anatomical Relations.—The salivary glands in man are three in number on each side—the parotid, the submaxillary, and the sublingual. The parotid gland communicates with the mouth by a large duct (Stenson's duct) which opens upon the inner surface of the cheek opposite the second molar tooth of the upper jaw. The submaxillary gland lies below the lower jaw, and its duct (Wharton's duct) opens into the mouth-cavity at the side of the frænum of the tongue. The sublingual gland lies in the floor of the mouth to the side of the frænum and opens into the mouth-cavity by a number (8 to 20) of small ducts, known as the ducts of Rivinus. One larger duct which runs parallel with the duct of Wharton and opens separately into the mouth-cavity is sometimes present in man. It is known as the duct of Bartholin and occurs normally in the dog. In addition to these three pairs of large glands a number of small glands belonging both to the albuminous and the

[1] Archiv für mikroskopische Anatomie, 1893, vol. 42, p. 82.

mucous types are found imbedded in the mucous membrane of the mouth and tongue. The secretions of these glands contribute to the formation of the saliva.

The course of the nerve-fibres supplying the large salivary glands is interesting in view of the physiological results of their stimulation. The description here given applies especially to their arrangement in the dog. The parotid gland receives its fibres from two sources—first, cerebral fibres which originate in the glosso-pharyngeal or ninth cranial nerve, pass into a branch of this nerve known as the tympanic branch or nerve of Jacobson, thence to the small superficial petrosal nerve, through which they reach the otic ganglion. From this ganglion they pass by way of the auriculo-temporal branch of the inferior max-
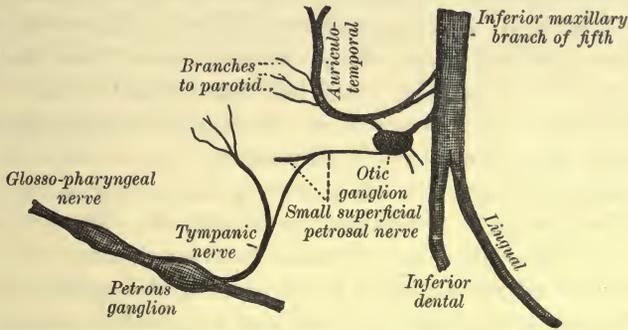
Fig. 68.—Schematic representation of the course of the cerebral fibres to the parotid gland.

illary division of the fifth cranial nerve to the parotid gland. (A schematic diagram showing the course of these fibres is given in Figure 68.) A second
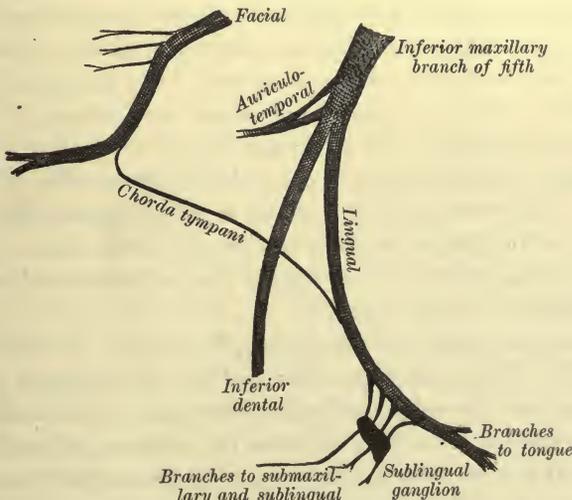
Fig. 69.—Schematic representation of the course of the chorda tympani nerve to the submaxillary gland.

supply of nerve-fibres is obtained from the cervical sympathetic nerve, the fibres reaching the gland ultimately in the coats of the blood-vessels. The

submaxillary (and the sublingual) glands receive their nerve-fibres also from two sources. The cerebral fibres arise from the brain in the facial nerve and pass out in the chorda tympani branch (Fig. 69). This latter nerve, after emerging from the tympanic cavity through the Glaserian fissure, joins the lingual nerve. After running with this nerve for a short distance, the secretory (and vaso-dilator) nerve-fibres destined for the submaxillary and sublingual glands branch off and pass to the glands, following the course of the ducts. Where the chorda tympani fibres leave the lingual there is a small ganglion which has received the name of submaxillary ganglion. The nervefibres to the glands pass through this ganglion, but Langley has shown that only those destined for the sublingual gland really connect with the nervecells of the ganglion, and he suggests therefore that it should be called the sublingual instead of the submaxillary ganglion. The nerve-fibres for the submaxillary gland make connections with nerve-cells within the hilus of the gland itself. The submaxillary and sublingual glands receive also sympathetic nerve-fibres, which after leaving the superior cervical ganglion pass to the glands in the coats of the blood-vessels.

Histological Structure.—The salivary glands belong to the type of compound tubular glands, as Flemming has pointed out. That is, the secreting portions are tubular in shape, although in cross sections these tubes may present various outlines according as the plane of the section passes through them. The parotid is described usually as a typical serous or albuminous gland. Its secreting epithelium is composed of cells which in the fresh condition as well as in preserved specimens contain numerous fine granules (see Figs. 70 and 72, *A*). Heidenhain states that in exceptional cases (in the dog) some of the secreting cells may belong to the mucous type. The basement membrane is composed of flattened branched connective-tissue cells, the interstices between which are filled by a thin membrane. The submaxillary gland differs in histology in different animals. In some, as the dog or cat, all the secretory tubes are composed chiefly or exclusively of epithelial cells of the mucous type (Fig. 73). In man the gland is of a mixed type, the secretory tubes containing both mucous and albuminous cells. The sublingual gland in man also contains both varieties of cells, although the mucous cells predominate. It follows from these histological characteristics that the secretion from the submaxillary and sublingual glands is thick and mucilaginous as compared with that from the parotid.

In the mucous glands another variety of cells, the so-called demilunes or crescent cells, is frequently met with; and the physiological significance of these cells has been the subject of much discussion. The demilunes are crescent-shaped granular cells lying between the mucous cells and the basement membrane, and not in contact, therefore, with the central lumen of the tube (see Fig. 73). According to Heidenhain these demilunes are for the purpose of replacing the mucous cells. In consequence of long-continued activity the mucous cells may disintegrate and disappear, and the demilunes then develop into new mucous cells. According to other views the demilunes represent

merely an inactive stage of ordinary mucous cells, or the basal protoplasmic part of a mucous cell, or, finally, a distinct secretory cell of the albuminous type.

The secreting tubules of the salivary glands each possess a distinct lumen round which the cells are arranged. In addition a number of recent observers, making use of the Golgi method of staining, have apparently demonstrated that in the albuminous glands the lumen is continued as fine capillary spaces running between the secreting cells.[1] The statement is also made that from these secretion capillaries small side-branches are given off which penetrate into the substance of the cell, making an intracellular origin of the system of ducts; this point, however, needs confirmation. In the mucous glands similar secretion capillaries are found only in connection with the demilunes. This latter fact supports the view that the demilunes are not simply inactive forms of mucous cells, but cells with a specific functional activity. It is an undoubted fact that the salivary glands possess definite secretory nerves which when stimulated start the formation of secretion. This fact indicates that there must be a direct contact of some kind between the gland-cells and the terminations of the secretory fibres. The nature of this connection has been the subject of numerous investigations, the results of which were for a long time negative or untrustworthy. Quite recently, however, the application of the useful Golgi method has led to satisfactory results. The ending of the nerve-fibres in the submaxillary and sublingual glands has been described by a number of observers.[2] The accounts differ somewhat as to details of the finer anatomy, but it seems to be clearly established that the secretory fibres from the chorda tympani end first round the intrinsic nerve-ganglion cells of the glands, and from these latter cells axis-cylinders are distributed to the secreting cells, passing to these cells along the ducts. The nerve-fibres terminate in a plexus upon the membrana propria of the alveoli, and from this plexus fine fibrils pass inward to end on and between the secreting cells. A more elaborate description of the final termination of the secretory fibres is given by Dogiel[3] for the lachrymal gland, which is a gland belonging to the albuminous type. It would seem from these observations that the nerve-fibrils do not penetrate or fuse with the gland-cells, as was formerly supposed, but form a terminal network in contact with the cells, following thus the general schema for the connection between nerve-fibres and peripheral tissues.

Composition of the Secretion.—The saliva as it is found in the mouth is a mixed secretion from the large salivary glands and the numerous smaller glands scattered over the mucous membrane of the mouth. It is a colorless or opalescent, turbid, and mucilaginous liquid of weakly alkaline reaction and a specific gravity of about 1003. It may contain numerous flat cells derived from the epithelium of the mouth, and the peculiar spherical cells known as salivary corpuscles, which seem to be altered leucocytes. The im-

[1] Laserstein: *Pflüger's Archiv für die gesammte Physiologie*, 1893, Bd. 55, p. 417.

[2] See Huber: *Journal of Experimental Medicine*, 1896, vol. i. p. 281.

[3] *Archiv für mikroscopische Anatomie*, 1893, Bd. xlii. S. 632.

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portant constituents of the secretion are mucin, a diastatic enzyme known as ptyalin, traces of albumin and of potassium sulphocyanide, and inorganic salts such as potassium and sodium chloride, potassium sulphate, sodium carbonate, and calcium carbonate and phosphate. The average proportions of these constituents is given in the following analysis by Hammerbacher:

Water, ...	994.203
Solids:	
Mucin and epithelial cells, ...	2.202
Ptyalin and albumin, ...	1.390
Inorganic salts, ...	2.205
	5.797
	1.000.000

(Potassium sulphocyanide, 0.041.)

Of the organic constituents of the saliva the albumin exists in small and variable quantities, and its exact nature is not determined. The mucin gives to the saliva its ropy, mucilaginous character. This substance belongs to the group of combined proteids, glyco-proteids (see section on Chemistry), consisting of a proteid combined with a carbohydrate group. The physiological value of this constituent seems to lie in its physical properties, as described in the section on Digestion. The most interesting constituent of the mixed saliva is the ptyalin. This body belongs to the group of enzymes or unorganized ferments, whose general and specific properties are described in the section on Digestion. It suffices here to say only that ptyalin belongs to the diastatic group of enzymes, whose specific action is to convert the starches into sugar by a process of hydrolysis. In some animals (dog) ptyalin seems to be normally absent from the fresh saliva. An interesting fact with reference to the saliva is the large quantity of gases, particularly CO_2, which may be obtained from it when freshly secreted. In an analysis by Pflüger of the saliva from the submaxillary gland the following figures were obtained: CO_2, 65 per cent., of which 42.5 per cent. was in the form of carbonates; N, 0.8 per cent.; O, 0.6 per cent. For the parotid secretion Külz reports: CO_2, 66.7 per cent., of which 62 per cent. was in combination as carbonate; N, 3.8 per cent.; O, 1.46 per cent.

The secretions of the parotid and submaxillary glands can be obtained easily by inserting a cannula into the openings of the ducts in the mouth. The secretion of the sublingual can only be obtained in sufficient quantities for analysis from the lower animals. Examination of the separate secretions shows that the main difference lies in the fact that the parotid saliva contains no mucin, while that of the submaxillary and especially of the sublingual gland is rich in mucin. The parotid saliva of man seems to be particularly rich in ptyalin as compared with that of the submaxillary, while the secretion of the latter and of the sublingual gland give a stronger alkaline reaction than the parotid saliva.

The Secretory Nerves.—The existence of secretory nerves was discovered by Ludwig in 1851. He found that stimulation of the chorda tympani nerve caused a flow of saliva from the submaxillary gland. He established also

several important facts with regard to the pressure and composition of the secretion which will be referred to presently. It was afterward shown that the salivary glands receive a double nerve-supply, in part by way of the cervical sympathetic and in part through cerebral nerves, as briefly described on p. 159. It was discovered also that not only are secretory fibres carried to the glands by these paths, but that the vaso-motor fibres are contained in the same nerves, and the arrangement of these latter fibres is such that the cerebral nerves contain vaso-dilator fibres which cause a dilatation of the small arteries in the glands and an accelerated blood-flow, while the sympathetic carries vaso-constrictor fibres whose stimulation causes a constriction of the small arteries and a diminished blood-flow. The effect upon the secretion of stimulation of these two sets of fibres is found to vary somewhat in different animals. For purposes of description we may confine ourselves to the effects observed on dogs, since most of our fundamental knowledge upon the subject is derived from Heidenhain's[1] experiments upon this animal. If the chorda tympani nerve is stimulated by weak induction shocks the gland begins to secrete promptly, and the secretion, by proper regulation of the stimuli, may be kept up for hours. The secretion thus obtained is thin and watery, flows freely, is abundant in amount, and contains not more than 1 or 2 per cent. of total solids. At the same time there is an increased flow of blood through the gland. The whole gland takes on a redder hue, the veins are distended, and if cut the blood that flows from them is of a redder color than in the resting gland, and may show a distinct pulse—all of which points to a dilatation of the small arteries. If now the sympathetic fibres are stimulated, quite different results are obtained. The secretion is relatively small in amount, flows slowly, is thick and turbid, and may contain as much as 6 per cent. of total solids. At the same time the gland becomes pale, and if the veins be cut the flow from them is slower than in the resting gland, thus indicating that a vaso-constriction has occurred.

The increased vascular supply to the gland accompanying the abundant flow of "chorda saliva" and the diminished flow of blood during the scanty secretion of "sympathetic saliva" suggest naturally the idea that the whole process of secretion may be at bottom a vaso-motor phenomenon, the amount of secretion depending only on the quantity and pressure of the blood flowing through the gland. It has been shown conclusively that this idea is erroneous and that definite secretory fibres exist. The following facts may be quoted in support of this statement: (1) Ludwig showed that if a mercury manometer is connected with the duct of the submaxillary gland and the chorda is then stimulated for a certain time, the pressure in the duct may become greater than the blood-pressure in the gland. This fact shows that the secretion is not derived entirely by processes of filtration from the blood. (2) If the blood-flow be shut off completely from the gland, stimulation of the chorda will still give a secretion for a short time. (3) If atropin is

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[1] *Pflüger's Archiv für die gesammte Physiologie*, 1878, Bd. xvii. p. 1; also in *Hermann's Handbuch der Physiologie*, 1883, Bd. v. Th. 1.

injected into the gland, stimulation of the chorda will cause vascular dilatation but no secretion. This may be explained by supposing that the atropin paralyzes the secretory but not the dilator fibres. (4) Hydrochlorate of quinine injected into the gland gives vascular dilatation but no secretion. In this case the secretory fibres are still irritable, since stimulation of the chorda gives the usual secretion.

A still more marked difference between the effect of stimulation of the cerebral and the sympathetic fibres may be observed in the case of the parotid gland in the dog. Stimulation of the cerebral fibres alone in any part of their course (see Fig. 68) gives an abundant thin and watery saliva, poor in solid constituents. Stimulation of the sympathetic fibres alone (provided the cerebral fibres have not been stimulated shortly before (Langley) and the tympanic nerve has been cut to prevent a reflex effect) gives usually no perceptible secretion at all. But in this last stimulation a marked effect is produced upon the gland, in spite of the absence of a visible secretion; this is shown by the fact that subsequent or simultaneous stimulation of the cerebral fibres gives a secretion very unlike that given by the cerebral fibres alone, in that it is very rich indeed in organic constituents. The amount of organic matter in the secretion may be tenfold that of the saliva obtained by stimulation of the cerebral fibres alone.

Another important and suggestive set of facts with regard to the action of the secretory nerves is obtained from a study of the differences in composition of the secretion following upon variations in the strength of stimulation of the nerves.

Relation of the Composition of the Secretion to the Strength of Stimulation.— If the stimulus to the chorda be gradually increased in strength, care being taken not to fatigue the gland, the chemical composition of the secretion is found to change with regard to the relative amounts of the water, the salts, and the organic material. The water and the salts increase in amount with the increased strength of stimulus up to a certain maximal limit, which for the salts is about 0.77 per cent. Increase of stimulus beyond this point has no further effect, the amount of water and salts remaining constant. It is important to observe that this effect may be obtained from a perfectly fresh gland as well as from a gland which had previously been secreting actively. With regard to the organic constituents the precise result obtained depends on the condition of the gland. If previous to the stimulation the gland was in a resting condition and unfatigued, then increased strength of stimulation is followed at first by a rise in the percentage of organic constituents, and this rise in the beginning is more marked than in the case of the salts. But with continued stimulation the increase in organic material soon ceases, and finally the amount begins actually to diminish, and may fall to a low point in spite of the stronger stimulation. On the other hand, if the gland in the beginning of the experiment had been previously worked to a considerable extent, then an increase in the stimulating current, while it increases the amount of water and salts, may have either no effect at all upon the organic

constituents or cause only a temporary increase, quickly followed by a fall. Similar results may be obtained from stimulation of the cerebral nerves of the parotid gland. The above facts led Heidenhain to believe that the conditions determining the secretion of the organic material are different from those controlling the water and salts, and he gave a rational explanation of the differences observed, in his theory of trophic and secretory fibres.

Theory of Trophic and Secretory Nerve-fibres.—This theory supposes that two physiological varieties of nerve-fibres are distributed to the salivary glands. One of these varieties controls the secretion of the water and inorganic salts and its fibres may be called secretory fibres proper, while the other, to which the name trophic is given, causes the formation of the organic constituents of the secretion, probably by a direct influence on the metabolism in the cell. Were the trophic fibres to act alone, the organic products would be formed within the cell but there would be no visible secretion, and this is the hypothesis which Heidenhain uses to explain the results of the experiment described above upon stimulation of the sympathetic fibres to the parotid of the dog. In this animal, apparently, the sympathetic branches to the parotid contain exclusively or almost exclusively trophic fibres, while in the cerebral branches both trophic and secretory fibres proper are present. The results of stimulation of the cerebral and sympathetic branches to the submaxillary gland of the same animal may be explained in terms of this theory by supposing that in the latter nerve trophic fibres preponderate, and in the former the secretory fibres proper.

It is obvious that this anatomical separation of the two sets of fibres along the cerebral and sympathetic paths may be open to individual variations, and that dogs may be found in which the sympathetic branches to the parotid glands contain secretory fibres proper, and therefore give some flow of secretion on stimulation. These variations might also be expected to be more marked when animals of different groups are compared. Thus Langley[1] finds that in cats the sympathetic saliva from the submaxillary gland is less viscid than the chorda saliva, just the reverse of what occurs in the dog. To apply Heidenhain's theory to this case it is necessary to assume that in the cat the trophic fibres run chiefly in the chorda. An interesting fact with reference to the secretion of the parotid in dogs has been noted by Langley and is of special interest, since, although it may be reconciled with the theory of trophic and secretory fibres, it is at the same time suggestive of an incompleteness in this theory. As has been said, stimulation of the sympathetic in the dog causes usually no secretion from the parotid. Langley[2] finds, however, that if the tympanic nerve is stimulated just previously, stimulation of the sympathetic causes a secretory flow from the parotid. One may explain this in terms of the theory by assuming that the sympathetic does contain a few secretory fibres proper, but that ordinarily their action is too feeble to start the flow of water. Previous stimulation of the tympanic nerve, however, leaves the gland-cells in

[1] *Journal of Physiology*, 1878, vol. i. p. 96.
[2] *Ibid.*, 1889, vol. x. p. 291.

a more irritable condition, so that the few secretory fibres proper in the sympathetic branches are now effective in producing a flow of water.

Theories of the Action of Trophic and Secretory Fibres.—The way in which the trophic fibres act has been briefly indicated. They may be supposed to set up metabolic changes in the protoplasm of the cells, leading to the formation of certain definite products, such as mucin or ptyalin. That such changes do occur is abundantly shown by microscopic examination of the resting and the active gland, the details of which will be given presently. In general these changes may be supposed to be katabolic in nature; that is, to consist in a disassociation or breaking down of the complex living material with the formation of the simpler and more stable organic constituents of the secretion. There is evidence to show that these gland-cells during activity form fresh material from the nourishment supplied by the blood; that is, that anabolic or building-up processes occur along with the katabolic changes. The latter are the more obvious and are the changes which are usually associated with the action of the trophic nerve-fibres. It is possible, also, that the anabolic or growth changes may be under the control of separate fibres for which the name anabolic fibres would be appropriate. Satisfactory proof of the existence of a separate set of anabolic fibres has not yet been furnished.

The method of action of the secretory fibres proper is difficult to understand. At present the theories suggested are very speculative, and a detailed account of them is scarcely appropriate in this place. Heidenhain's own view may be mentioned, but it should be borne in mind that it is only an hypothesis, the truth of which is far from being demonstrated. The theory starts from the fact that no more water leaves the blood-capillaries than afterward appears in the secretion; that is, no matter how long the secretion continues, the gland does not become œdematous nor does the velocity of the lymph-stream in the lymphatics of the gland increase. This being the case, we must suppose that the stream of water is regulated by the secretion, that is, by the activity of the gland-cells. If we suppose that some constituent of these cells has an attraction for water, then, while the gland is in the resting state, water will be absorbed from the basement membrane; this in turn supplies its loss from the surrounding lymph, and the lymph obtains the same amount of water from the blood. As the amount of water in the cell increases a point is reached at which the osmotic tension comes to an equilibrium, and the diffusion stream from blood to cells is at a standstill. The water in the cells does not escape into the lumen of the tubule or of the secretion capillaries, because the periphery of the cell is modified to form a layer offering considerable resistance to filtration. The action of the secretory fibres proper consists in so altering the structure of this limiting layer of the cells that it offers less resistance to filtration; consequently the water under tension in the cells escapes into the lumen, and the osmotic pressure of its substance again starts up a stream of water from capillaries to cells, which continues as long as the nerve-stimulation is effective.

Recent work by Ranvier, Drasch, Biedermann, and others has called attention to an interesting phenomenon occurring in gland-cells during secretion which when better known will possibly throw light upon the formation of the water stream under the influence of nerve-stimulation. Ranvier[1] describes in both serous and mucous cells the formation of vacuoles within the protoplasmic substance. These vacuoles are particularly abundant after nerve-stimulation. They seem to contain water, and if they behave as they do in the protozoa—and this is indicated by the observations of Drasch[2] upon the glands in the nictitating membrane in the frog—they would seem to form a mechanism sufficient to force water from the cells into the lumen.

Histological Changes during Activity.—The cells of both the albuminous and mucous glands undergo distinct histological changes in consequence of prolonged activity, and these changes may be recognized both in preparations from the fresh gland and in preserved specimens. In the parotid gland Heidenhain studied the changes in stained sections after hardening in alcohol. In the resting gland (Fig. 70) the cells are compactly filled with
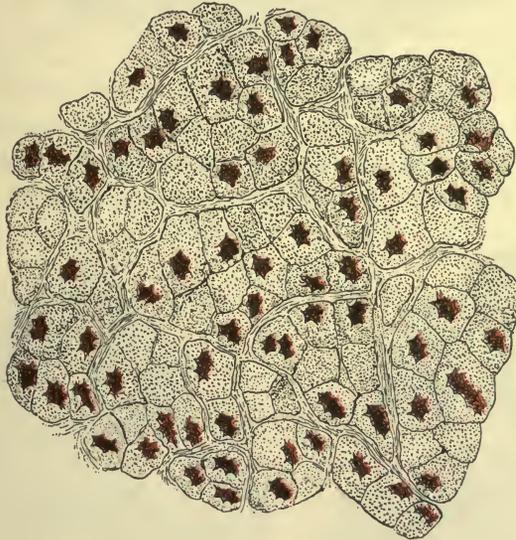
Fig. 70.—Parotid of the rabbit, in the resting condition (after Heidenhain).

granules which stain readily and are imbedded in a clear ground substance which does not stain. The nucleus is small and more or less irregular in outline. After stimulation of the tympanic nerve the cells show but little alteration, but stimulation of the sympathetic produces a marked change (Fig. 71). The cells become smaller, the nuclei more rounded and the granules are more closely packed. This last appearance seems, however, to be due to the hardening reagents used. A truer picture of what occurs may be obtained from a study of sections of the fresh gland. Langley,[3] who first used this method,

[1] *Comptes rendus,* cxviii., 4, p. 168. [2] *Archiv für Anatomie und Physiologie,* 1889, S. 96.
[3] *Journal of Physiology,* 1879, vol. ii. p. 260.

describes his results as follows: When the animal is in a fasting condition the
cells have a granular appearance throughout their substance, the outlines of
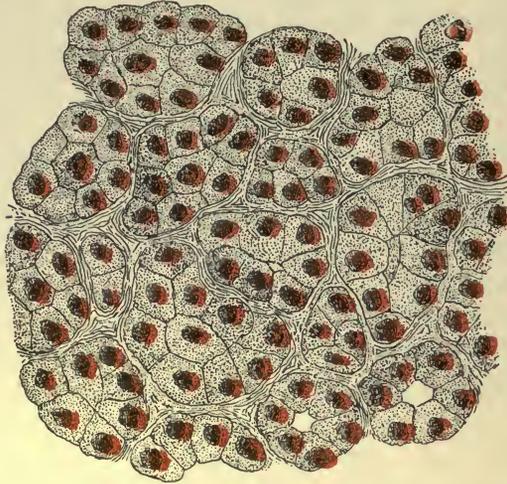
FIG. 71.—Parotid of the rabbit, after stimulation of the sympathetic (after Heidenhain).

the different cells being faintly marked by light lines (Fig. 72, *A*). When
the gland is made to secrete by giving the animal food, by injecting pilocarpin,
or by stimulating the sympathetic nerves, the granules begin to disappear from
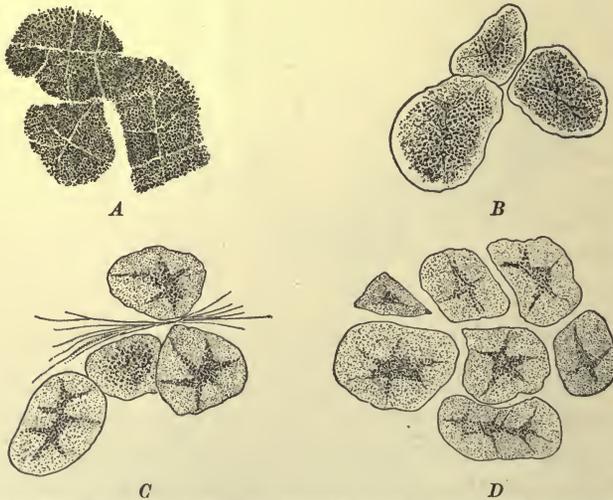
FIG. 72.—Parotid gland of the rabbit in a fresh state, showing portions of the secreting tubules: *A*, in
a resting condition; *B*, after secretion caused by pilocarpin; *C*, after stronger secretion, pilocarpin and
stimulation of sympathetic; *D*, after long-continued stimulation of sympathetic (after Langley).

the outer borders of the cells (Fig. 72, *B*), so that each cell now shows an outer
clear border and an inner granular one. If the stimulation is continued the
granules become fewer in number and are collected near the lumen and the mar-

gins of the cells, the clear zone increases in extent and the cells become smaller (Fig. 72, *C, D*). Evidently the granular material is used up in some way to make the organic material of the secretion. Since the ptyalin is a conspicuous organic constituent of the secretion, it is assumed that the granules in the resting gland contain the ptyalin, or rather a preliminary material from which the ptyalin is constructed during the act of secretion. On this latter assumption the granules are frequently spoken of as zymogen granules. During the act of secretion two distinct processes seem to be going on in the cell, leaving out of consideration for the moment the formation of the water and the salts. In the first place the zymogen granules undergo a change such that they are forced or dissolved out of the cell, and, second, a constructive metabolism or anabolism is set up, leading to the formation of new protoplasmic material from the substances contained in the blood and lymph. The new material thus formed is the clear, non-granular substance, which appears first toward the basal sides of the cells. We may suppose that the clear substance during the resting periods undergoes metabolic changes, whether of a katabolic or anabolic character cannot be safely asserted, leading to the formation of new granules, and the cells are again ready to form a secretion of normal composition. It should be borne in mind that in these experiments the glands were stimulated beyond normal limits. Under ordinary conditions the cells are probably never depleted of their granular material to the extent represented in the figures.

In the cells of the mucous glands changes equally marked may be observed after prolonged activity. In stained sections of the resting gland, according to Heidenhain, the cells are large and clear (Fig. 73), with flattened nuclei
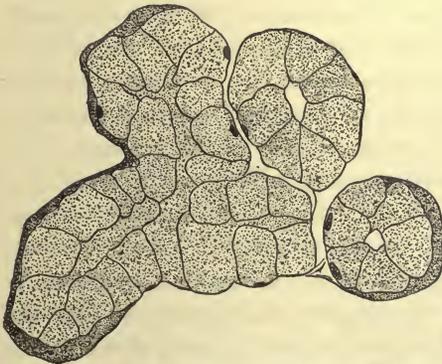
FIG. 73.—Mucous gland: submaxillary of dog; resting stage.
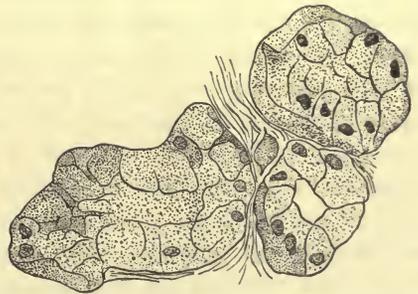
FIG. 74.—Mucous gland: submaxillary of dog after eight hours' stimulation of the chorda tympani.

placed well toward the base of the cell. When the gland is made to secrete the nuclei become more spherical and lie more toward the middle of the cell, and the cells themselves become distinctly smaller. After prolonged secretion the changes become more marked (Fig. 74) and, according to Heidenhain, some of the mucous cells may break down completely, the demilune cells increasing in size and forming new mucous cells. According to most of the

later observers, however, the mucous cells do not actually disintegrate, but form again new material during the period of rest as was described for the goblet cells of the intestine. In the mucous as in the albuminous cells observations upon pieces of the fresh gland seem to give more reliable results than those upon preserved specimens. Langley [1] has shown that in the fresh mucous cells of the submaxillary gland numerous large granules may be discovered, about 125 to 250 to a cell. These granules are comparable to those found in the goblet cells, and may be interpreted as consisting of mucin or some preparatory material from which mucin is formed. The granules are sensitive to reagents; addition of water causes them to swell up and disappear. It may be assumed that this happens during secretion, the granules becoming converted to a mucin-mass which is extruded from the cell.

Action of Atropin, Pilocarpin, and Nicotin upon the Secretory Nerves.—The action of drugs upon the salivary glands and their secretions belongs properly to pharmacology, but the effects of the three drugs mentioned are so decided that they have a peculiar physiological interest. Atropin in small doses injected either into the blood or into the gland-duct prevents the action of the cerebral fibres (tympanic nerve or chorda tympani) upon the glands. This effect may be explained by assuming that the atropin paralyzes the endings of the cerebral fibres in the glands. That it does not act directly upon the gland-cells themselves seems to be assured by the interesting fact that with doses sufficient to throw out entirely the secreting action of the cerebral fibres, the sympathetic fibres are still effective when stimulated. Pilocarpin has directly the opposite effect to atropin. In minimal doses it sets up a continuous secretion of saliva, which may be explained upon the supposition that it stimulates the endings of the secretory fibres in the gland. Within certain limits these drugs antagonize each other—that is, the effect of pilocarpin may be removed by the subsequent application of atropin and *vice versa*. Nicotin, according to the experiments of Langley,[2] prevents the action of the secretory nerves, not by action on the gland-cells or the endings of the nerve-fibres, but by paralyzing the nerve-ganglion cells through which the fibres pass on their way to the gland. If, for example, the superior cervical ganglion is painted with a solution of nicotin, stimulation of the cervical sympathetic below the gland will give no secretion; stimulation, however, of the fibres in the ganglion or between the ganglion and gland will give the usual effect. By the use of this drug Langley is led to believe that the cells of the so-called submaxillary ganglion are really intercalated in the course of the fibres to the sublingual gland, while the nerve-cells with which the submaxillary fibres make connection are found chiefly in the hilus of the gland itself.

Paralytic Secretion.—A remarkable phenomenon in connection with the salivary glands is the so-called paralytic secretion. It has been known for a long time that if the chorda tympani is cut the submaxillary gland after a cer-

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[1] *Journal of Physiology*, 1889, vol. x. p. 433.
[2] *Proceedings of the Royal Society*, London, 1889, vol. xlvi. p. 423.

tain time, one to three days, begins to secrete slowly and the secretion continues uninterruptedly for a long period—as long, perhaps, as several weeks—and eventually the gland itself undergoes atrophy. Langley [1] states that section of the chorda on one side is followed by a continuous secretion from the glands on both sides; the secretion from the gland of the opposite side he designates as the antiparalytic or antilytic secretion. He believes that this continuous secretion is due to the fact that the irritability of the nerve-cells in the secretion centre (see below) in the medulla, as well as of the nerve-cells in the gland itself, is so much increased that the venosity of the blood itself is sufficient to throw them into continuous activity. It is difficult, however, to understand why section of the chorda should have any such effect as this upon the medullary centre, especially as it is known that section of the secretory fibres in the sympathetic does not give a similar result. A more plausible explanation is the one suggested by Bradford,[2] namely, that the salivary glands receive through their cerebral nerves certain fibres which may be called anabolic, whose action is to cause suspension or inhibition of the katabolic changes in the gland-cells— probably, according to Bradford, by acting on the local nerve-ganglion cells in the gland. When these fibres are removed by section there is nothing to hold the katabolic processes in the gland in check, and as a result we get a continuous secretion and a wasting of the gland.

Normal Mechanism of Salivary Secretion.—Under normal conditions the flow of saliva from the salivary glands is the result of a reflex stimulation of the secretory nerves. The sensory fibres concerned in this reflex must be chiefly fibres of the glosso-pharyngeal and lingual nerves supplying the mouth and tongue. Sapid bodies and various other chemical or mechanical stimuli applied to the tongue or mucous membrane of the mouth will produce a flow of saliva. The normal flow during mastication must be effected by a reflex of this kind, the sensory impulse being carried to a centre and thence transmitted through the efferent nerves to the glands. It is found that section of the chorda prevents the reflex, in spite of the fact that the sympathetic fibres are still intact. No satisfactory explanation of the normal functions of the secretory fibres in the sympathetic has yet been given. Since the flow of saliva is normally a definite reflex, we should expect a distinct salivary secretion centre. This centre has been located by physiological means in the medulla oblongata; its exact position is not clearly defined, but possibly it is represented by the nuclei of origin of the secretory fibres which leave the medulla by way of the facial and glosso-pharyngeal nerves. Owing to the wide connections of nerve-cells in the central nervous system we should expect this centre to be affected by stimuli from various sources. As a matter of fact it is known that the centre and through it the glands may be called into activity by stimulation of the sensory fibres of the sciatic, splanchnic, and particularly the vagus nerves. So, too, various psychical acts, such as the thought of savory food and the feeling of nausea preceding vomiting, may be accompanied by a flow of saliva,

[1] *Proceedings of the Royal Society*, London, 1885, No. 236.
[2] *Journal of Physiology*, 1888, vol. ix. p. 287.

the effect in this case being due probably to stimulation of the secretion centre by nervous impulses descending from the higher nerve-centres. Lastly, the medullary centre may be inhibited as well as stimulated. The well-known effect of fear, embarrassment, or anxiety in producing a parched throat may be supposed to arise in this way by the inhibitory action of nerve-impulses arising in the cerebral centres.

Electrical Changes in the Gland during Activity.—It has been shown that the salivary as well as other glands suffer certain changes in electric potential during activity which are comparable in a general way to the "action currents" observed in muscles and nerves (see section on Muscle and Nerve). Bradford[1] has apparently shown that stimulation of the secretory fibres proper causes the surface of the gland to become negative to the hilus, while stimulation of the trophic fibres gives the reverse effect. Stimulation of a mixed nerve, therefore, such as the chorda, gives a diphasic effect. The theories bearing upon the causes of these electrical changes are too intricate and speculative to enter upon here. The reader is referred to a recent account by Biedermann[2] for further details.

C. Pancreas; Glands of the Stomach and Intestines.

Anatomical Relations of the Pancreas.—The pancreas in man lies in the abdominal cavity behind the stomach. It is a long, narrow gland, its head lying against the curvature of the duodenum and its narrow extremity or tail reaching to the spleen. The chief duct of the gland (duct of Wirsung) usually opens into the duodenum, together with the common bile-duct, about eight to ten centimeters below the pylorus. In some cases, at least, a smaller duct may enter the duodenum separately somewhat lower down. The points at which the ducts of the pancreas open into the duodenum vary considerably in different animals. For instance, in the dog there are two ducts, the larger of which enters the duodenum separately about six to seven centimeters below the pylorus, while in the rabbit the main duct opens into the duodenum over thirty centimeters below the pylorus. The nerves of the pancreas are derived from the solar plexus, but physiological experiments which will be described presently show that the gland receives fibres from at least two sources, through the vagus nerve and through the sympathetic system.

Histological Characters.—The pancreas, like the salivary glands, belongs to the compound tubular type. The cells in the secreting portions of the tubules, the so-called alveoli, resemble the serous or albuminous type, and are usually characterized by the fact that the outer portion of each cell, that is, the part toward the basement membrane, is composed of a clear non-granular substance which takes stains readily, while the inner portion turned toward the lumen is filled with conspicuous granules. In addition to this type of cell, which is the characteristic secreting element of the organ, the pancreas contains a number of irregular masses of cells of a different character (bodies of Langerhans). These latter cells are clear and small, frequently have ill-

[1] *Journal of Physiology*, 1887, vol. viii. p. 86.   [2] *Elektrophysiologie*, Jena, 1895

defined cell-bodies, but contain nuclei which stain readily with ordinary reagents. By some these cells are supposed to be immature secreting cells of the ordinary pancreatic type. By others it is thought that they are a separate type of cell and take some special part in the secretory functions of the pancreas. Nothing definite, however, is known as to their physiological importance.

In the pancreas, as in the salivary glands, the latest histological methods have apparently demonstrated that the lumen of each secreting tubule is continuous with a system of intercellular secretion capillaries lying between the secretory cells, and according to some observers sending terminal capillaries into the very substance of the gland-cells.

Composition of the Pancreatic Secretion.—The pancreatic secretion is a clear alkaline liquid which in some animals (dog) is thick and mucilaginous. Its physical characters seem to vary greatly, even in the same animal, according to the duration of the secretion or the time since the establishment of the fistula by which it is obtained (see p. 238). In a newly made fistula in the dog the secretion is thick, but in a permanent fistula it becomes much thinner and more watery. The main constituents of the secretion are three enzymes, a large percentage of proteid material the exact nature of which is not known, some fats, soaps, a slight amount of lecithin, and inorganic salts. The strongly alkaline nature seems to be due chiefly to sodium carbonate, which may be present in amounts equal to 0.2 to 0.4 per cent. The three enzymes are known respectively as trypsin, a proteolytic ferment; amylopsin, a diastatic ferment, and steapsin, a fat-spliting ferment. The action of these enzymes in digestion is described in the section on Digestion.

Action of the Nerves on the Secretion of the Pancreas.—In animals like the dog, in which the process of digestion is not continuous, the secretion of the pancreas is also supposed to be intermittent. A study of the flow of secretion as observed in cases of pancreatic fistula indicates that it is connected with the beginning of digestion in the stomach, and is therefore probably a reflex act. Until recently, however, little direct evidence had been obtained of the existence of secretory nerves. Stimulation of the medulla was known to increase the flow of pancreatic juice and to alter its composition as regards the organic constituents, but direct stimulation of the vagus and the sympathetic nerves gave only negative results. Lately, however, Pawlow[1] and some of his students have been able to overcome the technical difficulties in the way, and have given what seems to be perfectly satisfactory proof of the existence of distinct secretory fibres comparable in their nature to those described for the salivary glands. The results that they have obtained may be stated briefly as follows: Stimulation of either the vagus nerve or the sympathetic causes, after a considerable latent period, a marked flow of pancreatic secretion. The failure of other experiments to get this result was due apparently to the sensitiveness of the gland to variations in its blood-supply. Either direct or reflex vaso-con-

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[1] Pawlow: *Du Bois-Reymond's Archiv für Physiologie*, 1893, Suppl. Bd.; Mett: *Ibid.*, 1894; Kudrewetsky: *Ibid.*, 1894.

striction of the pancreas prevents the action of the secretory nerves upon it. Thus stimulation of the sympathetic gives usually no effect upon the secretion, because vaso-constrictor fibres are stimulated at the same time, but if the sympathetic nerve is cut five or six days previously, so as to give the vaso-constrictor fibres time to degenerate, stimulation will cause, after a long latent period, a distinct secretion of the pancreatic juice.

Accepting the theory of secretory and trophic fibres proposed for the salivary glands, the experiments upon the variations in pancreatic secretion following upon stimulation of the vagus and sympathetic respectively seem to indicate that in the sympathetic trophic fibres are more abundant, and in the vagus the secretory fibres proper. The long latent period elapsing between the time of stimulation and the effect upon the flow is not easily understood. The authors quoted give no satisfactory explanation of this curious fact, but suggest that it may be due to the presence of definite inhibitory fibres to the gland, which are stimulated simultaneously with the secretory fibres and thus hold the secretion in check for a time. No independent proof of the presence of inhibitory fibres is furnished.

Histological Changes during Activity.—The morphological changes in the pancreatic cells have long been known and have been studied satisfactorily in the fresh gland as well as in preserved specimens. The general nature of the changes is the same as that described for the salivary gland, and is illustrated in Figures 75, 76, and 77. If the gland is removed from a dog which has been fasting for about twenty-four hours and is hardened in alcohol and sectioned and stained, it will be found that the cells are filled with granules except for a narrow zone toward the basal end, which is marked off more clearly because it stains more deeply than the granular portion (Fig. 75). If, on the contrary, the gland is taken from a dog which had been fed
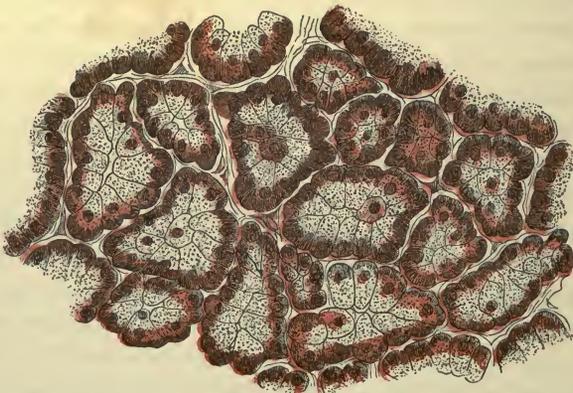
Fɪɢ. 75.—Pancreas of the dog during hunger; preserved in alcohol and stained in carmine (after Heidenhain).

six to ten hours previously, the non-staining granular zone is much reduced in size, while the clearer non-granular zone is enlarged (Fig. 76). The increase in size of the non-granular zone does not, however, entirely compensate for

the loss of the granular material, so that the cell as a whole is smaller in size than in the gland from the fasting animal. It seems evident that during the hours immediately following a meal—that is, at the time when we know
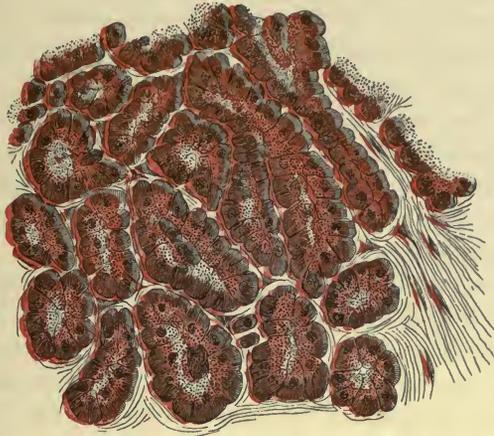
Fig. 76.—Pancreas of dog during first stage of digestion ; alcohol, carmine (after Heidenhain).

that the gland is discharging its secretion, the granular material is being used up. After the period of most active secretion—that is, during the tenth to the twentieth hour after a meal in the case of a dog fed once in twenty-four
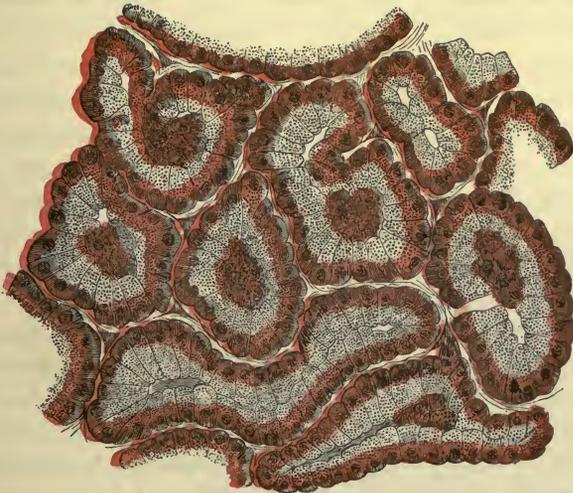
Fig. 77.—Pancreas of dog during second stage of digestion; alcohol, carmine (after Heidenhain).

hours—the gland-cells return to their resting condition (Fig. 77). New granules are formed, and finally, if the gland is left unstimulated they fill the entire cell except for a narrow margin at the basal end.

Similar results are reported by Kühne[1] and Lea from observations made upon the pancreas cells in a living rabbit. In the inactive gland the outlines

[1] *Untersuchungen aus dem physiologischen Institut des Universitäts Heidelberg,* 1882, Bd. ii.

of the individual cells are not clearly distinguishable, but it can be seen that there are two zones, one clear and homogeneous on the side toward the basement membrane, and one granular on the side toward the lumen. During activity the secretory tubules show a notched appearance correspondiug to the positions of the cells, the outlines of the cells become more distinct, the granular zone becomes smaller, and the homogeneous zone increases in width. It should be stated also that in this latter condition the basal zone of the cells shows a distinct striation. From these appearances we must believe that, as in the case of the salivary gland, a part at least of the organic material of the secretion is formed from the granules of the inner zone, and that the granules in turn are formed within the cells from the homogenous material of the outer zone.

Enzyme and Zymogen.—The observations just described indicate that the enzymes of the pancreatic secretion are derived from the granules in the cells, but other facts show that the granules do not contain the enzymes as such, but a preparatory material or mother-substance to which the name zymogen (enzyme-maker) is given. This belief rests upon facts of the following kind: If a pancreas is removed from a dog which has fasted for twenty-four hours, when, as we have seen, the cells are heavily loaded with granules, and a glycerin extract is made, very little active enzyme will be found in it. If, however, the gland is allowed to stand for twenty-four hours in a warm spot before the extract is made, or if it is first treated with dilute acetic acid, the glycerin extract will show very active tryptic or amylolytic properties. Moreover, if an inactive glycerin extract of the perfectly fresh gland is treated by various methods, such as dilution with water or shaking with finely divided platinum-black, it becomes converted to an active extract capable of digesting proteid material. These results are readily explained upon the hypothesis that the granules contain only zymogen material, which during the act of secretion, or by means of the methods mentioned, may be converted into the corresponding enzymes. As the three enzymes of the pancreatic secretion seem to be distinct substances, one may suppose that each has it own zymogen to which a distinctive name might be given. The zymogen which is converted into trypsin is frequently spoken of as trypsinogen.

Normal Mechanism of Pancreatic Secretion.—After the establishment of a pancreatic fistula it is possible to study the flow of secretion in its relations to the ingestion of food. Experiments of this kind have been made, and show that in animals like the dog, in which sufficient food may be taken in a single meal to last for a day, the flow of secretion is intimately connected with the reception of food into the stomach and its subsequent digestive changes. The time relations of the secretion to the ingestion of food are shown in the accompanying chart (Fig. 78). The secretion begins immediately after the food enters the stomach, and increases in velocity up to a certain maximum which is reached some time between the first and the third hour after the meal. The velocity then diminishes rapidly to the fifth or sixth hour, after which there may be a second smaller increase reaching its maximum about the ninth to the eleventh hour. From this point the secretion

diminishes in quantity to the sixteenth or seventeenth hour, when it has practically reached the zero point. In man, in whom the meals normally occur at intervals of five to six hours, this curve of course would have a different form. The interesting fact, however, that the secretion starts very soon
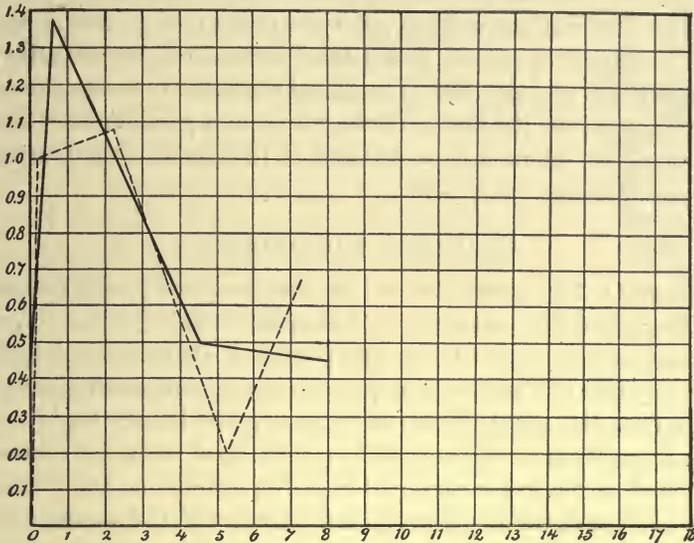
Fig. 78.—Curve of the secretion of pancreatic juice during digestion. The figures along the abscissa represent hours after the beginning of digestion; the figures along the ordinate represent the quantity of this secretion in cubic centimeters. Curves of two experiments are given (after Heidenhain).

after the beginning of gastric digestion is probably true for human beings, and gives strong indication that the secretion is a reflex act.

Recently a number of experiments have been reported which strengthen the view that the normal secretion of the pancreas is reflexly excited by stimuli acting upon the mucous membrane of the stomach or intestine. Gottlieb[1] finds that in rabbits the pancreatic secretion is very greatly accelerated by stimulants such as oil of mustard, pepper, acids, or alkalies introduced into the stomach or duodenum, and Dolinsky,[2] working upon dogs under more favorable experimental conditions finds that acids are particularly effective in arousing the pancreatic flow; on the contrary, alkalies in the stomach diminish the pancreatic secretion. Dolinsky believes that the normal acidity of gastric secretion is perhaps the most effective stimulus to the pancreatic gland, and that in this way the flow of gastric juice in ordinary digestion starts the pancreatic gland into activity. Whether the acid acts after absorption into the blood, or stimulates the sensory fibres of the mucous membrane and thus reflexly affects the pancreas through its secretory nerves, is not definitely known, but the probabilities are in favor of the latter view. It is probable also that the acid acts mainly upon the sensory fibres of the mucous membrane of the duodenum rather than upon the gastric membrane.

[1] *Archiv für experimentelle Pathologie und Pharmakologie,* 1894, Bd. 33, p. 273.
[2] *Archives des Sciences biologiques,* St. Petersburg, 1895, vol. iii. p. 399.

We are justified from these experiments in believing that the mechanism of the pancreatic secretion is closely analogous to that controlling the salivary glands. It is usually stated, however, that the pancreas still continues to secrete after all its extrinsic nerves have been severed. The experiments upon which this statement rests are not entirely satisfactory, since, owing to the way in which the nerve-fibres reach the organ in the walls of the blood-vessels, it is difficult to be sure that all the nerve-fibres are actually severed, and moreover it is probable that if the gland continues to secrete after removal of its extrinsic nerves, the flow is of the nature of a paralytic secretion, which in time would be followed by a wasting of the gland. More experimental work is required upon this point.

GLANDS OF THE STOMACH.

Histological Characteristics.—The glands of the gastric mucous membrane belong practically to the type of simple tubular glands; for, although two or more of the simple tubes may possess a common opening or mouth, there is no system of ducts such as prevails in the compound glands, and the divergence from the simplest form of tubular gland is very slight. Each of these glands possesses a relatively wide mouth, lined with the columnar epithelium found on the free surface of the gastric membrane, and a longer, narrower secreting part, which penetrates the thickness of the mucosa and is lined by cuboidal cells. The glands in the pyloric end of the stomach differ in general appearance from those in the fundic end, and are especially characterized by the fact that they possess only one kind of secretory cell, while the fundic glands contain two apparently distinct types of cells (Fig. 81). The lumen in the latter glands is lined by a continuous layer of short cylindrical cells to which Heidenhain gave the name of chief-cells. These cells are apparently concerned in the formation of pepsin, the proteolytic enzyme contained in the gastric secretion. In addition there are present a number of cells of an oval or triangular shape which are placed close to the basement membrane and do not extend quite to the main lumen of the gland. These cells, which are not found in the pyloric glands, are known by various names, such as border-cells, parietal cells, oxyntic cells, etc. The last-mentioned name has been given to them because of their supposed connection with the formation of the acid of the gastric secretion. The nature and function of these border-cells have been the subject of much discussion. From the histological side they have been interpreted as representing either immature forms of the chief-cell, or else the active modification of this cell. Recent work, however, seems to have demonstrated that they form a specific type of cell, and probably therefore have a specific function. An interesting histological fact in connection with the parietal cells is that, in the human stomach at least, they frequently contain several nuclei, five or six, and some of these seem to be derived from ingested leucocytes. They are interesting also in the fact that they contain distinct vacuoles which seem to appear some time after digestion has begun, reach a maximum size, and then gradually grow smaller and finally disappear. Like the similar phenomenon

described for other gland-cells (p. 167), this appearance is possibly connected with the formation of the secretion.

The duct of a gastric gland was formerly supposed to be a simple tube extending the length of the gland. A number of recent observers, however, have shown, by the use of the Golgi stain, that this view is not entirely correct, at least not for the glands in the fundus in which border-cells are present. In these glands the central lumen sends off side channels which pass to the border-cells and there form a network of small capillaries which lie either in or round the cell.[1] An illustration of the duct-system of a fundic gland is given in Figure 79. If this work is correct it would seem that the chief-cells communicate directly with the central lumen, but that the border-cells have a system of secretion capillaries of their own, resembling in this respect the demilunes of the mucous salivary glands (p. 161). This

Fig. 79.—Ducts and secretion capillaries to parietal cells. Gland from the fundus of cat's stomach (after Langendorff and Laserstein).

fact tends to corroborate the statement previously made, that the border-cells form a distinct type of cell whose function is probably different from that of the chief-cells.

Composition of the Secretion of the Gastric Mucous Membrane.— The secretion as it is poured out on the surface of the mucous membrane is composed of the true secretion of the gastric glands together with more or less mucus, which is added by the columnar cells lining the surface of the membrane and the mouths of the glands. In addition to the mucus, water, and inorganic salts, the secretion contains as its characteristic constituents hydrochloric acid and two enzymes—namely, pepsin which acts upon proteids, and rennin which has a specific coagulating effect upon the casein of milk. For an analysis of the gastric secretion of the dog see p. 161. According to Heidenhain,[2] the secretion from the pyloric end of the stomach is characterized by the absence of hydrochloric acid, although it still contains pepsin. This statement rests upon careful experiments in which the pyloric end was entirely resected and made into a blind pouch which was then sutured to the abdominal wall to form a fistula. In this way the secretion of the pyloric end could be obtained free from mixture with the secretion of any other part of the alimentary canal. By this means Heidenhain found that the pyloric secretion is an alkaline liquid containing pepsin. This fact forms the strongest evidence for Heidenhain's hypothesis that the HCl of the normal gastric secretion is produced by the "border-cells" of the fundic glands and the pepsin by the "chief-cells," since HCl is formed only in parts of the stomach containing border-cells, whereas the pepsin is produced in the pyloric end, where only chief-cells are present.

Evidence of this character is naturally not very convincing, and the hypoth-

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[1] Langendorff and Laserstein : *Pflüger's Archiv für die gesammte Physiologie*, 1894, Bd. lv. S. 578.

[2] *Archiv für die gesammte Physiologie*, 1878, Bd. xviii. S. 169, also Bd. xix.

esis, especially that part connecting the border-cells with the formation of HCl, can only be accepted provisionally until further investigation confirms or disproves it. It should be stated that the alkalinity of the secretion obtained from the pyloric glands by Heidenhain's method has been attributed by some authors to the abnormal conditions prevailing, especially to the section of the vagus fibres which necessarily results from the operation. Contejean[1] asserts that the reaction of the pyloric membrane under normal conditions is acid in spite of the absence of border-cells.

Influence of the Nerves upon the Gastric Secretion.—It has been very difficult to obtain direct evidence of the existence of extrinsic secretory nerves to the gastric glands. In the hands of most experimenters, stimulation of the vagi and of the sympathetics has given negative results, and, on the other hand, section of these nerves does not seem to prevent the formation of the gastric secretion. There are on record, however, a number of observations which point to a direct influence of the central nervous system on the secretion. Thus Bidder and Schmidt found that in a hungry dog with a gastric fistula (page 225) the mere sight of food caused a flow of gastric juice; and Richet reports a case of a man in whom the œsophagus was completely occluded and in whom a gastric fistula was established by surgical operation. It was then found that savory foods chewed in the mouth produced a marked flow of gastric juice. There would seem to be no other way of explaining the secretions in these cases except upon the supposition that they were caused by a reflex stimulation of the gastric mucous membrane through the central nervous system. These cases are strongly supported by some recent experimental work on dogs by Pawlow[2] and Schumowa-Simanowskaja. These observers used dogs in which a gastric fistula had been established, and in which, moreover, the œsophagus had been divided in the neck and the upper and lower cut surfaces brought to the skin and sutured so as to make two fistulous openings. In these animals, therefore, food taken into the mouth and subsequently swallowed escaped to the exterior through the upper œsophageal fistula, without entering the stomach. Nevertheless this "fictitious meal," as the authors designate it, in the case of certain foods (meats), brought about an increased formation of gastric juice, although, curiously enough, other foods, such as milk and soup, gave negative results. If in such animals the two vagi were cut, the "fictitious meal" no longer caused a secretion of the gastric juice, and this fact may be considered as showing that the secretion obtained when the vagi were intact was due to a reflex stimulation of the stomach through these nerves. Finally, these observers were able to show that direct stimulation of the vagi under proper conditions causes, after a long latent period (six or seven minutes), a marked secretion of gastric juice. A satisfactory explanation of the unusually long latent period is not given.

Taking these results together, we must believe that the vagi send secretory fibres to the gastric glands, and that these fibres may be stimulated reflexly

[1] *Archives de Physiologie*, 1892, p. 554.
[2] *Du Bois-Reymond's Archiv für Physiologie*, 1895, S. 53.

through the sensory nerves of the mouth, and probably also by psychical states.

Normal Mechanism of Secretion of the Gastric Juice.—Our knowledge of the means by which the flow of gastric secretion is caused during normal digestion, and of the varying conditions which influence the flow, is as yet quite incomplete. Some notable experiments recently made by Pawlow [1] and Khigine, together with older experiments by Heidenhain,[2] have, however, thrown some light upon this difficult problem, and have, moreover, opened the way for further experimental study of the matter. Heidenhain cut out a part of the fundus of the stomach, converted it into a blind sac, and brought one end of the sac to the abdominal wall so as to form a fistulous opening to the exterior. The continuity of the stomach was established by suturing the cut ends, but the fundic sac was completely separated from the rest of the alimentary canal. He found that under these conditions the ingestion of ordinary food caused a secretion in the isolated and empty fundic sac, the secretion beginning fifteen to thirty minutes after the food was taken, and continuing until the stomach was empty. The ingestion of water caused a temporary secretion in the fundus, while indigestible material such as ligamentum nuchæ gave no secretion at all. Heidenhain's interpretation of these experiments as applied to normal secretion was that in ordinary digestion we must distinguish between a primary and a secondary secretion. The primary secretion depends upon the mechanical stimulus of the ingested food, and is confined to the spots directly stimulated ; the secondary secretion begins after absorption from the stomach is in progress, and involves the whole secreting surface. In the experiments related above, the secretion from the isolated fundus was a part of this secondary secretion. The stimulus in this case would seem to be a chemical one, consisting of some of the products absorbed from the stomach, which either acts directly on the gastric glands or indirectly on the intrinsic nerve-centres of the stomach.

Khigine has made similar experiments, but altered the operation so that the isolated fundic sac retained its normal nerve-supply, which in Heidenhain's operations was apparently injured. The results which he obtained are much more complete than any hitherto reported. He was able in the first place to determine the effect of various diets upon the amount of gastric secretion, upon its acidity, and upon its digestive power, using the secretion from the isolated fundic sac as typical of what was going on in the rest of the stomach in which the food was actually in process of digestion. One of his curves showing the effect of a mixed diet (milk, 600 cubic centimeters ; meat, 100 grams ; bread, 100 grams) is reproduced in Figure 80. It will be seen that the secretion began shortly after the ingestion of food (seven minutes) and increased rapidly to a maximum which it reached in two hours. After the second hour the flow decreased rapidly and nearly uniformly to about the tenth hour. The acidity also rose slightly between the first and second hours, and then fell gradually.

[1] Khigine: *Archives des Sciences biologiquè*, St. Petersburg, 1895, vol. iii. p. 461.

[2] *Hermann's Handbuch der Physiologie*, 1883, Bd. v. S. 114.

The digestive power showed a striking increase between the second and third hours. The author gives other tables showing the effect of a meat diet, a milk diet, a bread diet, etc., which seem to show that a meat diet promotes the greatest flow of secretion, while the bread diet gives a secretion of more than usual digestive power.

Khigine attempted to determine the effect of various chemical substances, found in food or occurring during digestion, upon the flow of the secretion, hoping by this means to throw some light upon the nature of the normal stimulus in ordinary gastric digestion. He obtained practically negative results with acids, alkalies, and neutral salts; none of these substances when introduced into the stomach had any decisive effect upon the secretion in the isolated fundus. Water, however, was quite effective; the ingestion of 500 cubic centimeters produced a marked and fairly long-continued secretion of gastric juice. But, so far as his experiments went, peptone is, *par excellence,* the chemical stimulus to the

FIG. 80.—Diagram showing the variation in quantity of gastric secretion in the dog after a mixed meal; also the variations in acidity and in digestive power (after Khigine).

gastric glands. The peptones caused an unusual secretion of gastric juice, although the closely related products of digestion known as proteoses (see p. 230) had little or no effect. It remains unsettled, however, how the water and the peptones act—whether they are absorbed, as Heidenhain thought, and act as chemical stimuli to the glands or the intrinsic ganglia of the stomach, or whether, as Khigine believes, they are direct and as it were specific nerve-stimuli to the sensory nerve-fibres of the mucous membrane, and thus produce a reflex effect upon the efferent secretory nerves to the gastric glands. The latter view would be more in accord with the mechanism of secretion as we know it in the salivary glands and pancreas, but it cannot be said to have been demonstrated as yet.

Histological Changes in the Gastric Glands during Secretion.—The cells of the gastric glands, especially the so-called chief-cells, show distinct changes as the result of prolonged activity. Upon preserved specimens taken from dogs fed at intervals of twenty-four hours, Heidenhain found that in the

fasting condition the chief-cells were large and clear, that during the first six hours of digestion the chief-cells as well as the border-cells increased in size, but that in a second period extending from the sixth to the fifteenth hour, the chief-cells became gradually smaller, while the border-cells remained large or even increased in size. After the fifteenth hour the chief-cells increased in size, gradually passing back to the fasting condition (see Fig. 81).

Fig. 81.—Glands of the fundus (dog): *A* and *A*[1], during hunger, resting condition; *B*, during the first stage of digestion; *C* and *D*, the second stage of digestion, showing the diminution in the size of the "chief" or central cells (after Heidenhain).

Langley[1] has succeeded in following the changes in a more satisfactory way by observations made directly upon the living gland. He finds that the chief-cells in the fasting stage are charged with granules, and that during digestion the granules are used up, disappearing first from the base of the cell, which then becomes filled with a non-granular material. Observations similar to those made upon the pancreas demonstrate that these granules represent in all probability a preliminary material from which the gastric enzymes are made during the act of secretion. The granules, therefore, as in the other glands, may be spoken of as zymogen granules, the preliminary material of the pepsin being known as pepsinogen and that of the rennin sometimes as pexinogen.

[1] *Journal of Physiology*, 1880, vol. iii. p. 269.

Glands of the Intestine.—At the very beginning of the intestine in the immediate neighborhood of the pylorus is found a small area of mucous membrane containing distinct tubular glands known usually as the glands of Brunner. These glands resemble closely in arrangement those of the pyloric end of the stomach, with the exception that the tubular duct is more branched. The secreting cells are similar to those of the pyloric glands of the stomach. Little is known of their secretion. According to some authors it contains pepsin. The amount of secretion furnished by these glands would seem to be too small to be of great importance in digestion. Throughout the length of the small and large intestine the well-known crypts of Lieberkühn are found. These structures resemble the gastric glands in general appearance, but not in the character of the epithelium. The epithelium lining the crypts is of two varieties—the goblet cells, whose function is to form mucus, and columnar cells with a characteristic striated border. The changes in the goblet cells during secretion and the probability of a relationship between them and the neighboring epithelial cells has been discussed (see p. 157). Whether or not the crypts form a definite secretion has been much debated. Physiologists are accustomed to speak of an intestinal juice, " succus entericus," as being formed by the glands of Lieberkühn, but practically nothing is known as to the mechanism of the secretion. The succus entericus itself, however it may be formed, can be collected by isolating small loops of the intestine and bringing the ends to the abdominal wall to form fistulous openings. The secretion thus obtained contains diastatic and also inverting ferments, the action of which is described on p. 247. Histologically, the cells in the bottom of the crypts do not possess the general characteristics of secreting cells.

D. LIVER; KIDNEY.

The liver is a gland belonging to the compound tubular type. The hepatic cells represent the secretory cells and the bile-ducts carry off the external secretion, which is designated as bile. In addition it is known that the liver-cells occasion important changes in the material brought to them in the blood, and that two important compounds, namely, glycogen and urea, are formed under the influence of these cells and afterward are given off to the blood-stream. The liver, then, furnishes a conspicuous example of a gland which forms simultaneously an external and an internal secretion. In this section we have to consider only certain facts in relation to the external secretion, the bile.

Histological Structure.—The general histological relations of the hepatic lobules need not be repeated in detail. It will be remembered that in each lobule the hepatic cells are arranged in columns radiating from the central vein, and that the intralobular capillaries are so arranged with reference to these columns that each cell is practically brought into contact with a mixed blood derived in part from the portal vein and in part from the hepatic artery.

As a gland making an external secretion, the relations of the liver-cells to

the ducts and to the nervous system are important points to be determined. The bile-ducts can be traced without difficulty to the fine interlobular branches running round the periphery of the lobules, but the finer branches or bile-capillaries springing from the interlobular ducts and penetrating into the interior of the lobules have been difficult to follow with exactness, especially as to their connection with the interlobular ducts on the one hand, and with the liver-cells on the other. The bile-capillaries have long been known to penetrate the columns of cells in the lobule in such a way that each cell is in contact with a bile-capillary at one point of its periphery, and with a blood-capillary at another, the bile- and blood-capillaries being separated from each other by a portion of the cell-substance. But whether or not intracellular branches from these capillaries actually penetrate into the substance of the liver-cells has been a matter in dispute. Kuppfer contended that delicate ducts arising from the capillaries enter into the cells and end in a small intracellular vesicle. As this appearance was obtained by forcible injections through the bile-ducts, it was thought by many to be an artificial product; but recent observations with staining reagents tend to substantiate the accuracy of Kuppfer's observations and confirm the belief that normally the system of bile-ducts begins within the liver-cells in minute channels which connect directly with the bile-capillaries.

Two questions with reference to the bile-ducts have given rise to considerable discussion and investigation : first, the relationship existing between the liver-cells and the lining epithelium of the bile-ducts; second, the presence or absence of a distinct membranous wall for the bile-capillaries. Different opinions are still held upon these points, but the balance of evidence seems to show that the bile-capillaries have no proper wall. They are simply minute tubular spaces penetrating between the liver-cells and corresponding to the alveolar lumen in other glands. Where the capillaries join the interlobular ducts the liver-cells pass gradually or abruptly, according to the class of vertebrates examined, into the lining epithelium of the ducts. From this standpoint, then, the liver-cells are homologous to the secreting cells of other glands in their relations to the general lining epithelium. Several observers (MaCallum,[1] Berkeley,[2] and Korolkow[3]) have claimed that they are able to trace nerve-fibres to the liver-cells, thus furnishing histological evidence that the complex processes occurring in these cells are under the regulating control of the central nervous system. According to the latest observers (Berkeley, Korolkow) the terminal nerve-fibrils end between the liver-cells, but do not actually penetrate the substance of the cells, as was described in some earlier papers. If these observations prove to be entirely correct they would demonstrate the direct effect of the nervous system on some at least of the manifold activities of the liver-cells. So far as the formation of the bile is concerned we have no satisfactory physiological evidence that it is under the control of the nervous system.

Composition of the Secretion.—The bile is a colored secretion. In

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[1] MaCallum : *Quarterly Journal of the Microscopical Sciences*, 1887, vol. xxvii. p. 439.
[2] Berkeley : *Anatomischer Anzeiger*, 1893, Bd. viii. S. 769.   [3] Korolkow : *Ibid.*, S. 750.

most carnivorous animals it is golden red, while in the herbivora it is green, the difference depending on the character and quantity of the pigments. In man the bile is usually stated to follow the carnivorous type, showing a reddish or brownish color, although in some cases apparently the green predominates. The characteristic constituents of the bile are the pigments, *bilirubin* in carnivorous bile and *biliverdin* in herbivorous bile, and the bile acids or bile-salts, the sodium salts of glycocholic or taurocholic acid, the relative proportions of the two acids varying in different animals. In addition there is present a considerable quantity of a mucoid nucleo-albumin, a constituent which is not formed in the liver-cells, but is added to the secretion by the mucous membrane of the bile-ducts and gall-bladder; and small quantities of cholesterin, lecithin, fats, and soaps. The inorganic constituents comprise the usual salts—chlorides, phosphates, carbonates and sulphates of the alkalies or alkaline earths. Iron is found in small quantities, combined probably as a phosphate. The secretion contains also a considerable though variable quantity of CO_2 gas, held in such loose combination that it can be extracted with the gas-pump without the addition of acid. The presence of this constituent serves as an indication of the extensive metabolic changes occurring in the liver-cells. Quantitative analyses of the bile show that it varies greatly in composition even in the same species of animal. Examples of this variability are given in the analyses quoted in the section on Digestion (p. 261), where a brief account will also be found of the origin and physiological significance of the different constituents.

The Quantity of Bile Secreted.—Owing to the fact that a fistula of the common bile-duct or gall-bladder may be established upon the living animal and the entire quantity of bile be drained to the exterior without serious detriment to the animal's life, we possess numerous statistics as to the daily quantity of the secretion formed. Surgical operations upon human beings (see p. 261 for references), made necessary by occlusion of the bile-passages, have furnished similar data for man. In round numbers the quantity in man varies from 600 to 800 cubic centimeters per day, or, taking into account the weight of the individuals concerned, about 8 to 16 cubic centimeters for each kilogram of body-weight. Observations upon the lower animals indicate that the secretion is proportionally greater in smaller animals. This fact is clearly shown in the following table, compiled by Heidenhain [1] for three herbivorous animals:

	Sheep.	Rabbit.	Guinea-pig.
Ratio of bile-weight for 24 hours to body-weight . . .	1 : 37.5	1 : 8.2	1 : 5.6
Ratio of bile-weight for 24 hours to liver-weight . . .	1.507 : 1	4.064 : 1	4.467 : 1

There seems to be no doubt that the bile is a continuous secretion, although in animals possessing a gall-bladder the secretion may be stored in this reservoir and ejected into the duodenum only at certain intervals connected with the processes of digestion. The movement of the bile-stream within the system of bile-ducts—that is, its actual ejection from the liver, is also probably intermittent. The observations of Copeman and Winston on a human patient

[1] *Hermann's Handbuch der Physiologie,* vol. v. Thl. 1, p. 253.

with a biliary fistula showed that the secretion was ejected in spirts, owing doubtless to contractions of the muscular walls of the larger bile-ducts. But though continuously formed within the liver-cells, the flow of bile is subject to considerable variations. According to most observers the activity of secretion is definitely connected with the period of digestion. Somewhere from the third to the fifth hour after the beginning of digestion there is a very marked acceleration of the flow, and a second maximum at a later period, ninth to tenth hour (Hoppe-Seyler), has been observed in dogs. The mechanism controlling the accelerated flow during the third to the fifth hour is not perfectly understood. It would seem to be correlated with the digestive changes occurring in the intestine, but whether the relationship is of the nature of a reflex nervous act, or whether it depends on increased blood-flow through the organ or upon some action of the absorbed products of secretion remains to be determined. It has been shown that the presence of bile in the blood acts as a stimulus to the liver-cells, and it is highly probable that the absorption of bile from the intestine which occurs during digestion serves to accelerate the secretion; but this circumstance obviously does not account for the marked increase observed in animals with biliary fistulas, since in these cases the bile does not reach the intestine at all. Some imperfect observations by Bidder and Schmidt indicate that the total quantity of bile varies with the character of the food, being larger upon a meat diet than when the subject is fed exclusively upon fats. Exact data as to the effect of the different food-stuffs are lacking.

Relation of the Secretion of Bile to the Blood-flow in the Liver.—Numerous experiments have shown that the quantity of bile formed by the liver varies more or less directly with the quantity of blood flowing through the organ. The liver-cells receive blood from two sources, the portal vein and the hepatic artery. The supply from both these sources is probably essential to the perfectly normal activity of the cells, but it has been shown that bile continues to be formed, for a time at least, when either the portal or the arterial supply is occluded. However, there can be little doubt that the material actually utilized by the liver-cells in the formation of their external and internal secretions is brought to them mainly by the portal vein, and that variations in the quantity of this supply influences directly the amount of bile produced. Thus, occlusion of some of the branches of the portal vein diminishes the secretion; stimulation of the spinal cord diminishes the secretion, since, owing to the large vascular constriction produced thereby in the abdominal viscera, the quantity of blood in the portal circulation is reduced; section of the spinal cord also diminishes the flow of bile or may even stop it altogether, since the result of such an operation is a general paralysis of vascular tone and a general fall of blood-pressure and velocity; stimulation of the cut splanchnic nerves diminishes the secretion because of the strong constriction of the blood-vessels of the abdominal viscera and the resulting diminution of the quantity of the blood in the portal circulation; section of the splanchnics alone, however, is said to increase the quantity of bile, in dogs, since in this case the paralysis of vascular tone is localized in the abdominal viscera. The effect of such a local dilatation of

the blood-vessels would be to diminish the resistance along the intestinal paths, and thus lead to a greater flow of blood to that area and the portal circulation.

In all these cases one might suppose that the greater or less quantity of bile formed depended only on the blood-pressure in the capillaries of the liver lobules—that so far at least as the water of the bile is concerned it is produced by a process of filtration and rises and falls with the blood-pressure. That this simple mechanical explanation is not sufficient seems to be proved by the fact that the pressure of bile within the bile-ducts, although comparatively low, may exceed that of the blood in the portal vein. While it is not possible, therefore, to exclude entirely the factor of filtration, it is evident that the quantity of secretion depends largely on the mere quantity of blood flowing by the cells in a unit of time.

The Existence of Secretory Nerves to the Liver.—The numerous experiments that have been made to ascertain whether or not the secretion of bile is under the direct control of secretory nerves have given unsatisfactory results. The experiments are difficult, since stimulation of the nerves supplying the liver, such as the splanchnic, is accompanied by vaso-motor changes which alter the blood-flow to the organ and thus introduce a factor which in itself influences the amount of the secretion. So far as our actual knowledge goes, the physiological evidence is against the existence of secretory nerve-fibres controlling the formation of bile. On the other hand, there are some experiments,[1] although they are not perfectly conclusive, which indicate that the glycogen formation within the liver-cells is influenced by a special set of *glyco-secretory* nerve-fibres. This fact, however, does not bear directly upon the formation of bile.

Motor Nerves of the Bile-vessels.—Doyon[2] has recently shown that the gall-bladder as well as the bile-ducts is innervated by a set of nerve-fibres comparable in their general action to the vaso-constrictor and vaso-dilator fibres of the blood-vessels. According to this author, stimulation of the peripheral end of the cut splanchnics causes a contraction of the bile-ducts and gall-bladder, while stimulation of the central end of the same nerve, on the contrary, brings about a reflex dilatation. Stimulation of the central end of the vagus nerve causes a contraction of the gall-bladder and at the same time an inhibition of the sphincter muscle closing the opening of the common bile-duct into the duodenum. These facts need confirmation, perhaps, on the part of other observers, although they are in accord with what is known of the actual movement of the bile-stream. The ejection of bile from the gall-bladder into the duodenum is produced by a contraction of the gall-bladder, and it is usually believed that this contraction is brought about reflexly from some sensory stimulation of the mucous membrane of the duodenum or stomach. The result of the experiments made by Doyon would indicate that the afferent fibres of this reflex pass upward in the vagus, while the efferent

[1] Morat and Dufourt: *Archives de Physiologie*, 1894, p. 371.
[2] *Archives de Physiologie*, 1894, p. 19.

fibres to the gall-bladder run in the splanchnics and reach the liver through the semilunar plexus.

Normal Mechanism of the Bile-secretion.—Bearing in mind the fact that our knowledge of the secretion of bile is in many respects incomplete, and that any theory of the act is therefore only provisional, we might picture the processes concerned in the secretion and ejection of bile as follows: The bile is steadily formed by the liver-cells and turned out into the bile-capillaries; its quantity varies with the quantity and composition of the blood flowing through the liver, but the formation of the secretion depends upon the activities taking place in the liver-cells, and these activities are independent of direct nervous control. During the act of digestion the formation of bile is increased, owing probably to a greater blood-flow through the organ and to the generally increased metabolic activity of the liver-cells occasioned by the inflow of the absorbed products of digestion. The bile after it gets into the bile-ducts is moved onward partly by the accumulation of new bile from behind, the secretory force of the cells, and partly by the contractions of the walls of the bile-vessels. It is stored in the gall-bladder, and at intervals during digestion is forced into the duodenum by a contraction of the muscular walls of the bladder, the process being aided by the simultaneous relaxation of a sphincter-like layer of muscle which normally occludes the bile-duct at its opening into the intestine; both these last acts are under the control of a nervous reflex mechanism.

Effect of Complete Occlusion of the Bile-duct.—It is an interesting fact that when the flow of bile is completely prevented by ligation of the bile-duct, the stagnant liquid is not reabsorbed by the blood directly, but by the lymphatics of the liver. The bile-pigments and bile-acids in such cases may be detected in the lymph as it flows from the thoracic duct. In this way they get into the blood, producing a jaundiced condition. The way in which the bile gets from the bile-ducts into the hepatic lymphatics is not definitely known, but probably it is due to a rupture, caused by the increased pressure, at some point in the course of the delicate bile-capillaries.

KIDNEY.

Histology.—The kidney is a compound tubular gland. The constituent uriniferous tubules composing it may be roughly separated into a secreting part comprising the capsule, convoluted tubes, and loop of Henle, and a collecting part, the so-called straight collecting-tube, the epithelium of which is assumed not to have any secretory function. Within the secreting part the epithelium differs greatly in character in different regions; its peculiarities may be referred to briefly here so far as they seem to have a physiological bearing, although for a complete description reference must be made to some work on Histology.

The arrangement of the glandular epithelium in the capsule with reference to the blood-vessels of the glomerulus is worthy of special attention. It will be remembered that each Malpighian corpuscle consists of two principal parts,

a tuft of blood-vessels, the glomerulus, and an enveloping expansion of the uniferous tubule, the capsule. The glomerulus is a remarkable structure (see Fig. 82, *A*). It consists of a small afferent artery which after entering the glomerulus breaks up into a number of capillaries, which, though twisted together, do not anastomose. These capillaries unite to form a single efferent vein of a smaller diameter than the afferent artery. The whole structure,
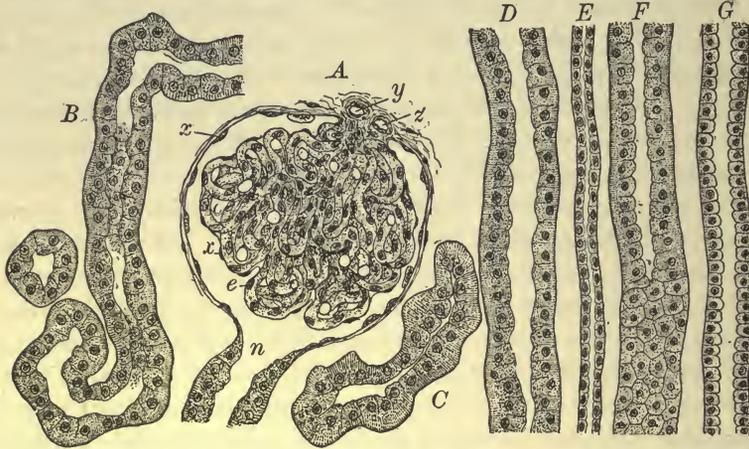
FIG. 82.—Portions of the various divisions of the uriniferous tubules drawn from sections of human kidney: *A*, Malpighian body; *x*, squamous epithelium lining the capsule and reflected over the glomerulus; *y, z*, afferent and efferent vessels of the tuft; *e*, nuclei of capillaries; *n*, constricted neck marking passage of capsule into convoluted tubule; *B*, proximal convoluted tubule; *C*, irregular tubule; *D* and *F*, spiral tubules; *E*, ascending limb of Henle's loop; *G*, straight collecting tubule (Piersol).

therefore, is not an ordinary capillary area, but a *rete mirabile,* and the physical factors are such that within the capillaries of the rete there must be a greatly diminished velocity of the blood-stream owing to the great increase in the width of the stream-bed and a high blood-pressure as compared with ordinary capillaries. Surrounding this glomerulus is the double-walled capsule. One wall of the capsule is closely adherent to the capillaries of the glomerulus; it not only covers the structure closely, but dips into the interior between the small lobules into which the glomerulus is divided. This layer of the capsule is composed of flattened endothelial-like cells, the glomerular epithelium, to which great importance is now attached in the formation of the secretion. It will be noticed that between the interior of the blood-vessels of the glomerulus and the cavity of the capsule which is the beginning of the uriniferous tubule there are interposed only two very thin layers, namely, the epithelium of the capillary wall and the glomerular epithelium. The apparatus would seem to afford most favorable conditions for filtration of the liquid parts of the blood. The epithelium clothing the convoluted portions of the tubule, including under this designation the so-called irregular and spiral portions and the loop of Henle, is of a character quite different from that of the glomerular epithelium (Fig. 82, *B, C, D, E, F, G*). The cells, speaking generally, are cuboidal or cylindrical, protoplasmic, and granular in appearance; on the side toward the basement membrane they often show a peculiar striation, while on the lumen side the extreme

periphery presents a compact border which in some cases shows a cilia-like striation. These cells have the general appearance of active secretory structures, and recent theories of urinary secretion attribute this importance to them.

Composition of Urine.—The chemical composition of the urine is very complex, as we should expect it to be when we remember that it contains most of the end-products of the varied metabolism of the body, its importance in this respect being greater than the other excretory organs such as the lungs, skin, and intestine. The secretion is a yellowish liquid which in carnivorous animals and in man has normally an acid reaction, owing to the presence of acid salts (acid sodium and acid calcium phosphate), and an average specific gravity of 1017 to 1020. The quantity formed in twenty-four hours is about 1200 to 1700 cubic centimeters. In the very young the amount of urine formed is proportionately much greater than in the adult. The normal urine contains about 3.4 to 4 per cent. of solid material, of which over half is organic material. Among the important organic constituents of the urine are the following : urea, uric acid, hippuric acid, xanthin, hypoxanthin, guanin, creatinin and aromatic oxy- acids (para-oxyphenyl propionic acid and para-oxyphenyl acetic acid, as simple salts or combined with sulphuric acid); phenol, paracresol, pyrocatechin and hydrochinon, these four substances being combined with sulphuric or glycuronic acid ; indican or indoxyl sulphuric acid ; skatol sulphuric acid ; oxalic acid ; sulphocyanides, etc. These and other organic constituents occurring under certain conditions of health or disease in various animals, are of the greatest importance in enabling us to follow the metabolism of the body. Something as to their origin and significance will be found in the section on Nutrition, while their purely chemical relations are described in the section on Chemistry.

Among the inorganic constituents of the urine may be mentioned sodium chloride, sulphates, phosphates of the alkalies and alkaline earths, nitrates, and carbon dioxide gas partly in solution and partly as carbonate. In this section we are concerned only with the general mechanism of the secretion of urine, and in this connection have to consider mainly the water and soluble inorganic salts and the typical nitrogenous excreta, namely, urea and uric acid.

The Secretion of Urine.—The kidneys receive a rich supply of nerve-fibres, but most histologists have been unable to trace any connection between these fibres and the epithelial cells of the kidney tubules. Berkeley[1] has, however, recently discovered nerve-fibres passing through the basement membrane and ending between the secretory cells.

The majority of purely physiological experiments upon direct stimulation of the nerves going to the kidney are adverse to the theory of secretory fibres, the marked effects obtained in these experiments being all explicable by the changes produced in the blood-flow through the organ. Two general theories of urinary secretion have been proposed. Ludwig held that the urine is formed by the simple physical processes of filtration and diffusion. In the glomeruli the conditions are most favorable to filtration, and he supposed that in these struc-

[1] *The Johns Hopkins Hospital Bulletin,* vol. iv., No. 28, p. 1.

tures water filtered through from the blood, carrying with it not only the inorganic salts, but also the specific elements (urea) of the secretion. There was thus formed at the beginning of the uriniferous tubules a complete but diluted urine, and in the subsequent passage of this liquid along the convoluted tubes it became concentrated by diffusion with the lymph surrounding the outside of the tubules. So far as the latter part of this theory is concerned it has not been supported by actual experiments; recent histological work (see below) seems to indicate that the epithelial cells of the convoluted tubules have a distinct secretory function, and that they give material to the secretion rather than take from it.

Bowman's theory of urinary secretion, which has since been vigorously supported and extended by Heidenhain, was based apparently mainly on histological grounds. It assumes that in the glomeruli water and inorganic salts are produced, while the urea and related bodies are eliminated through the activity of the epithelial cells in the convoluted tubes.

Elimination of Urea and Related Bodies.—Numerous facts have been discovered which tend to support the latter part of Bowman's theory—namely, the participation of the cells of the convoluted tubules in the secretion of the specific nitrogenous elements. In birds the main nitrogenous element of the secretion is uric acid instead of urea, and it is possible, owing to the small solubility of the urates, to see them as solid deposits in microscopic sections of the kidney. When the ureters are ligated the deposition of the urates in the kidney may become so great as to give the entire organ a whitish appearance. Nevertheless histological examinations of a kidney in this condition shows that the urates are found always in the tubes and never in the Malpighian corpuscles. From this result we may conclude that the uric acid is eliminated through the epithelial cells of the tubes. Heidenhain has shown by a striking series of experiments that the cells of the tubes possess an active secretory power. In these experiments a solution of indigo-carmine was injected into the circulation of a living animal after its spinal cord had been cut to reduce the blood-pressure and therefore the rapidity of the secretion. After a certain interval the kidneys were removed and the indigo-carmine precipitated *in situ* in the kidney by injecting alcohol into the blood-vessels. It was found that the pigment granules were deposited in the convoluted tubes, but never in the Malpighian corpuscles.

Still further proof of definite secretory functions on the part of the cells of the tubules is given by the results of recent histological work upon the changes in the cells during activity. Van der Stricht[1] and Disse[2] both describe definite morphological changes in the epithelial cells of the convoluted tubes and ascending loop of Henle which they connect with the functional activity of the cells. The details of the descriptions differ, but the two authors agree in finding that the material of the secretion collects in the interior of the

[1] *Comptes rendus,* 1891, and *Travail du Laboratoire d'Histologie de l' Université de Gand,* 1892.
[2] *Referate und Beiträge zur Anatomie und Entwickelungsgeschichte* (anatomische Hefte), Merkel and Bonnet, 1893.

cell to form a vesicle which is afterward discharged into the lumen of the cell. According to Disse the inactive cells are small and granular, and toward the lumen show a striated border of minute processes, while the lumen of the tube is relatively wide. As the fluid secretion accumulates in the cells it may be distinguished as a clear vesicular area near the nucleus. The cells enlarge and project toward the lumen, which becomes smaller; the striated border disappears. Finally the swollen cells fill the entire canal, and the liquid secretion is emptied from the cells by filtration. Van der Stricht believes that the vesicles rupture the cells and thus are cast out into the lumen. In longitudinal sections various stages in the process may be seen scattered along the length of a single tubule.

Secretion of the Water and Salts.—There seems to be no question that the elimination of water together with inorganic salts, and probably still other soluble constituents, takes place chiefly through the glomerular epithelium. This supposition is made in both the general theories that have been mentioned. It has, however, long been a matter of controversy, in this as in other glands, whether the water is produced by simple filtration or whether the glomerular epithelium takes an active part of some character in setting up the stream of water. The problem is perhaps simpler in this case than in the salivary glands, since the direct participation of secretory nerves in the process is excluded. On the filtration theory the quantity of urine should vary directly with the blood-pressure in the glomerulus. This relationship has been accepted as a crucial test of the validity of the filtration theory, and numerous experiments have been made to ascertain whether it invariably exists. Speaking broadly, any general rise of blood-pressure in the aorta will occasion a greater blood-flow and greater pressure in the glomerular vessels provided the kidney arteries themselves are not simultaneously constricted to a sufficient extent to counteract this favorable influence; whereas a general fall of pressure should have the opposite influence both on pressure and velocity of flow. It has been shown experimentally that if the general arterial pressure falls below 40 or 50 millimeters of mercury, as may happen after section of the spinal cord in the cervical region, the secretion of the urine will be greatly slowed, or suspended completely. Constriction of the small arteries in the kidney, whether effected through its proper vaso-constrictor nerves or by partially clamping its arteries, causes a diminution in the secretion and at the same time in all probability a fall of pressure within the glomeruli and a diminution in the total flow of blood. On the other hand, dilatation of the arteries of the kidney, whether produced through its vaso-dilator fibres or by section or inhibition of its constrictor fibres, augments the flow of urine and at the same time probably increases the pressure within the glomerular capillaries, and also the total quantity of blood flowing through them in a unit of time. From these and other experimental facts it is evident that the amount of secretion and the amount of pressure within the glomerular vessels do often vary together, and this relationship has been used to prove that the water of the secretion is obtained by filtration from the blood-plasma. But it will be

observed that the quantity of secretion varies not only with the pressure of the blood within the glomeruli, but also with the quantity of blood flowing through them.   Heidenhain has insisted that it is this latter factor and not the intracapillary pressure which determines the quantity of water secreted. He believes that the glomerular epithelial cells possess the property of actively secreting water, and that they are not simply passive filters; that the formation, in other words, is not a simple mechanical process, but a more complex one depending upon the living structure and properties of the epithelial cells. In support of this view he quotes the fact that partial compression of the renal veins quickly slows or stops altogether the flow of urine.   Compression of the veins should raise the pressure within the vessels of the glomeruli, and upon the filtration hypothesis should increase rather than diminish the secretion.   It has been shown also that if the renal artery is compressed for a short time so as to completely shut off the blood-flow to the kidney the secretion is not only suspended during the closure of the arteries but for a long time after the circulation is re-established.   According to Tiegerstedt, if the renal artery is ligated for only half a minute the activity of the kidney is suspended for three-quarters of an hour.   This fact is difficult to understand if the glomerular epithelium is simply a filtering membrane, but it is easily explicable upon the hypothesis that the epithelial cells are actively concerned in the production of the water.

Much of the recent work upon the secretion of urine tends to support Heidenhain's opinion.   Munk[1] and Senator made careful experiments upon excised kidneys which were kept alive and in functional activity by an artificial supply of blood, and were able to show that the quantity of the secretion depended less on the blood-pressure than on the rate of flow.   So, numerous experiments upon the action of diuretics[2] such as $NaCl$, KNO_3, and caffein seem to have shown distinctly that the increased flow of blood caused by these substances cannot be explained upon the filtration hypothesis, and that we must suppose that they have a specific action upon the kidney-cells, particularly the epithelial cells covering the glomeruli.

We may assume, therefore, until the contrary is proved, that the larger part of the water and inorganic salts of the urine is secreted at the capsular end of the uriniferous tubule by a definite action of the living epithelial cells. It must be borne in mind, however, that some water and probably also some of the inorganic salts are secreted at other parts of the tubule along with the elimination of the nitrogenous wastes.   It is of interest to add that the most important of the abnormal constituents of the urine under pathological conditions, such as the albumin in albuminuria, the hæmoglobin in hæmoglobinuria, and the sugar in glycosuria, seem likewise to escape from the blood into the kidney tubules through the glomerular epithelium.

Theoretical Considerations.—Granting that the glomerular epithelium

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[1] *Virchow's Archiv für pathologische Anatomie und Physiologie*, etc., Bd. cxiv., 1888.

[2] See Von Schroeder: *Archiv für exper. Pathologie und Pharmakol.*, Bd. **xxiv**. S. 85, and Dreser, *Ibid.*, 1892, Bd. **xxix**. S. 303.

takes an active part in directing the stream of water from the blood to the uriniferous tubules, it is natural to ask by what mechanism this action is effected. The problem is essentially similar to that already encountered in explaining the flow of water in other glands (see p. 166). There is as yet no satisfactory explanation given. It is to be supposed that this property is dependent upon some physical or chemical reaction of the substance of the cell, and involves the existence of no form of energy not already known to us in other ways; but what the nature of these reactions is must be left for future work. The extent of the activity seems to depend mainly on the quantity of blood flowing through the glomeruli. The greater the quantity of blood, the greater will be the quantity of water brought to the cells, and the more complete also the supply of needful oxygen. In addition, substances, such as the inorganic salts, which occur normally in the blood, or other substances which may be introduced therapeutically, may act as chemical irritants to these cells, and thus increase their secretory activity. The normal stimulus to the epithelial cells of the convoluted tubules, using the term convoluted to include the actively secreting parts, seems to be the presence of urea and related substances in the blood (lymph). That the elimination of the urea is not a simple act of diffusion seems to be clearly shown by the fact that its percentage in the blood is much less than in the urine. In some way the urea is selected from the blood and passed into the lumen of the tubule, and although we have microscopic evidence that this process involves very active changes in the substance of the cells, there is no adequate theory of the nature of the force which attracts the urea from the surrounding lymph. The whole process must be rapidly effected by the cell, since there is normally no heaping up of urea in the kidney-cells; the material is eliminated into the tubules as quickly as it is received from the blood. The rate of elimination increases normally with the increase in the urea in the blood, as would be expected upon the assumption that the urea itself acts as the physiological stimulus to the epithelial cells.

The Blood-flow through the Kidneys.—It will be seen from the discussion above that, other conditions remaining the same, the secretion of the kidney varies with the quantity of blood flowing through it. It is therefore important at this point to refer briefly to the nature and especially the regulation of the blood-flow through this organ, although the same subject is referred to in connection with the general description of vaso-motor regulation (see Circulation). It has been shown by Landergren[1] and Tiegerstedt that the kidney is a very vascular organ, at least when it is in strong functional activity such as may be produced by the action of diuretics. They estimate that in a minute's time, under the action of diuretics, an amount of blood flows through the kidney equal to the weight of the organ; this is an amount from four to nineteen times as great as occurs in the average supply of the other organs in the systemic circulation. Taking both kidneys into account, their figures show that (in strong diuresis) 5.6 per cent. of the total quantity of

[1] *Skandinavisches Archiv für Physiologie*, 1892, Bd. iv. S. 241.

blood sent out of the left heart in a minute may pass through the kidneys, although the combined weight of these organs makes only 0.56 per cent. of that of the body.

The richness of the supply of vaso-motor nerves to the kidney and the conditions which bring them into activity are fairly well known, owing to the useful invention of the oncometer by Roy.[1] This instrument is in principle a plethysmograph especially modified for use upon the kidney of the living animal. It is a kidney-shaped box of thin brass made in two parts, hinged at the back, and with a clasp in front to hold them together. In the interior of the box thin peritoneal membrane is so fastened to each half that a layer of olive oil may be placed between it and the brass walls. There is thus formed in each half a soft pad of oil upon which the kidney rests. When the kidney, freed as far as possible from fat and surrounding connective tissue, but with the blood-vessels and nerves entering at the hilus entirely uninjured, is laid in one-half of the oncometer, and the other half is shut down upon it and tightly fastened, the organ is surrounded by oil in a box which is liquid-tight at every point except one, where a tube is led off to some suitable recorder such as a tambour. Under these conditions every increase in the volume of the kidney will cause a proportional outflow of oil from the oncometer, which will be measured by the recorder, and every diminution in volume will be accompanied by a reverse change. At the same time the flow of urine during these changes can be determined by inserting a cannula into the ureter and measuring directly the outflow of urine. By this and other means it has been shown that the kidney receives a rich supply of vaso-constrictor nerve-fibres which reach it between and round the entering blood-vessels. These fibres emerge from the spinal cord chiefly in the lower thoracic spinal nerves (tenth to thirteenth in the dog), pass through the sympathetic system, and reach the organ as non-medullated fibres. Stimulation of these nerves causes a contraction of the small arteries of the kidney, a shrinkage in volume of the whole organ as measured by the oncometer, and a diminished secretion of urine. When, on the other hand, these constrictor fibres are cut as they enter the hilus of the kidney, the arteries are dilated on account of the removal of the tonic action of the constrictor fibres, the organ enlarges, and a greater quantity of blood passes through it, since the resistance to the blood-flow is diminished while the general arterial pressure in the aorta remains practically the same. Along with this greater flow of blood there is a marked increase in the secretion of urine.

Under normal conditions we must suppose that these fibres are brought into play to a greater or less extent by reflex stimulation, and thus serve to control the blood-flow through the kidney and thereby influence its functional activity. It has been shown, too, that the kidney receives vaso-dilator nerve-fibres, that is, fibres which when stimulated directly or reflexly cause a dilatation of the arteries, and therefore a greater flow of blood through the organ. According to Bradford,[2] these fibres emerge from the spinal cord mainly in the

[1] See Cohnheim and Roy : *Virchow's Archiv*, 1883, Bd. 92, S. 424.
[2] *Journal of Physiology*, 1889, vol. x. p. 358.

anterior roots of the eleventh, twelfth, and thirteenth spinal nerves. Under normal conditions these fibres are probably thrown into action by reflex stimulation and lead to an increased functional activity. It will be seen, therefore, that the kidneys possess a local nervous mechanism through which their secretory activity may be increased or diminished by corresponding alterations in the blood-supply. So far as is known, this is the only way in which the secretion in the kidneys can be directly affected by the central nervous system. It should be borne in mind, also, that the blood-flow through the kidneys, and therefore their secretory activity, may be affected by conditions influencing general arterial pressure. Conditions such as asphyxia, strychnin-poisoning, or painful stimulation of sensory nerves, which cause a great rise of blood-pressure, influence the kidney in the same way, and tend, therefore, to diminish the flow of blood through it; while conditions which lower general arterial pressure, such as general vascular dilatation of the skin vessels, may also depress the secretory action of the kidney by diminishing the amount of blood flowing through it.

In what way any given change in the vascular conditions of the body will influence the secretion of the kidney depends upon a number of factors, and their relations to one another; but any change which will increase the difference in pressure between the blood in the renal artery and the renal vein will tend to augment the flow of blood unless it is antagonized by a simultaneous constriction in the small arteries of the kidney itself. On the contrary, any vascular dilatation of the vessels in the kidney will tend to increase the blood-flow through it unless there is at the same time such a general fall of blood-pressure as is sufficient to lower the pressure in the renal artery and reduce the driving force of the blood to an extent that more than counteracts the favorable influence of diminished resistance in the small arteries.

Movements of the Ureter and the Bladder.—(See Micturition, p. 327.)

E. CUTANEOUS GLANDS; INTERNAL SECRETIONS.

The sebaceous glands, sweat-glands, and mammary glands are all true epidermal structures, and may therefore be conveniently treated together.

Sebaceous Secretion.—The sebaceous glands are simple or compound alveolar glands found over the cutaneous surface usually in association with the hairs, although in some cases they occur separately, as, for instance, on the prepuce and glans penis, and on the lips. When they occur with the hairs the short duct opens into the hair-follicle, so that the secretion is passed out upon the hair near the point where it projects from the skin. The alveoli are filled with cuboidal or polygonal epithelial cells, which are arranged in several layers. Those nearest the lumen of the gland are filled with fatty material. These cells are supposed to be cast off bodily, their detritus going to form the secretion. New cells are formed from the layer nearest the basement membrane, and thus the glands continue to produce a slow but continuous secretion. The sebaceous secretion, or sebum, is an oily semi-liquid material which sets upon exposure to the air to a cheesy mass, as is seen in the comedones or pim-

ples which so frequently occur upon the skin from occlusion of the opening of the ducts. The exact composition of the secretion is not known. It contains fats and soaps, some cholesterin, albuminous material, part of which is a nucleo-albumin often described as a casein, remnants of epithelial cells, and inorganic salts. The cholesterin occurs in combination with a fatty acid and is found in especially large quantities in sheep's wool, from which it is extracted and used commercially under the name of lanolin. The sebaceous secretion from different places, or in different animals, is probably somewhat variable in composition as well as in quantity. The secretion of the prepuce is known as the *smegma præputii;* that of the external auditory meatus, mixed with the secretion of the neighboring sweat-glands or ceruminous glands, forms the well-known ear-wax or *cerumen.* The secretion in this place contains a reddish pigment of a bitterish-sweet taste, the composition of which has not been investigated. Upon the skin of the newly-born the sebaceous material is accumulated to form the *vernix caseosa.* The well-known uropygal gland of birds is homologous with the mammalian sebaceous glands, and its secretion has been obtained in sufficient quantities for chemical analysis. Physiologically it is believed that the sebaceous secretion affords a protection to the skin and hairs. Its oily character doubtless serves to protect the hairs from becoming too brittle, or, on the other hand, from being too easily saturated with external moisture. In this way it probably aids in making the hairy coat a more perfect protection against the effect of external changes of temperature. Upon the surface of the skin also it forms a thin protective layer which tends to prevent undue loss of heat from evaporation, and possibly is important in other ways in maintaining the physiological integrity of the external surface.

Sweat.—The sweat or perspiration is a secretion of the sweat-glands. These latter structures are found over the entire cutaneous surface except in the deeper portions of the external auditory meatus. They are particularly abundant upon the palms of the hands and the soles of the feet. Krause estimates that their total number for the whole cutaneous surface is about two millions. In man they are formed on the type of simple tubular glands; the terminal portion contains the secretory cells, and at this part the tube is usually coiled to make a more or less compact knot, thus increasing the extent of the secreting surface. The larger ducts have a thin muscular coat of involuntary tissue which may possibly be concerned in the ejection of the secretion. The secretory cells in the terminal portion are columnar in shape, they possess a granular cytoplasm and are arranged in a single layer. The amount of secretion formed by these glands varies greatly, being influenced by the condition of the atmosphere as regards temperature and moisture, as well as by various physical and psychical states such as exercise and emotions. An average quantity for twenty-four hours is said to vary between 700 and 900 grams, although this amount may be doubled under certain conditions.

Composition of the Secretion.—The precise chemical composition of sweat is difficult to determine, owing to the fact that as usually obtained it is liable

to be mixed with the sebaceous secretion. Normally it is a very thin secretion of low specific gravity (1004) and an alkaline reaction, although when first secreted the reaction may be acid owing to admixture with the sebaceous material. The larger part of the inorganic salts consists of sodium chloride. Small quantities of the alkaline sulphates and phosphates are also present. The organic constituents, though present in mere traces, are quite varied in number. Urea, uric acid, creatinin, aromatic oxy- acids, ethereal sulphates of phenol and skatol, and albumin, are said to occur when the sweating is profuse. Argutinsky has shown that after the action of vapor-baths, and as the result of muscular work, the amount of urea eliminated in this secretion may be considerable (see p. 299). Under pathological conditions involving a diminished elimination of urea through the kidneys it has been observed that the amount found in the sweat is markedly increased, so that crystals of it may be deposited upon the skin. Under perfectly normal conditions, however, it is obvious that the organic constituents are of minor importance. The main fact to be considered in the secretion of sweat is the formation of water.

Secretory Fibres to the Sweat-glands.—Definite experimental proof of the existence of sweat-nerves was first obtained by Goltz[1] in some experiments upon stimulation of the sciatic nerve in cats. In the cat and dog, in which sweat-glands occur only on the balls of the feet, the presence of sweat-nerves may be demonstrated with great ease. Electrical stimulation of the peripheral end of the divided sciatic nerve, if sufficiently strong, will cause visible drops of sweat to form on the hairless skin of the balls of the feet. When the electrodes are kept at the same spot on the nerve and the stimulation is maintained the secretion soon ceases, but this effect seems to be due to a temporary injury of some kind to the nerve-fibres at the point of stimulation, and not to a genuine fatigue of the sweat-glands or the sweat-fibres, since moving the electrodes to a new point on the nerve farther toward the periphery calls forth a new secretion. The secretion so formed is thin and limpid, and has a marked alkaline reaction. The anatomical course of these fibres has been worked out in the cat with great care by Langley.[2] He finds that for the hind feet they leave the spinal cord chiefly in the first and second lumbar nerves, enter the sympathetic chain, and emerge from this as non-medullated fibres in the gray rami proceeding from the sixth lumbar to the second sacral ganglion, but chiefly in the seventh lumbar and first sacral, and then join the nerves of the sciatic plexus. For the fore feet the fibres leave the spinal cord in the fourth to the tenth thoracic nerves, enter the sympathetic chain, pass upward to the first thoracic ganglion, whence they are continued as non-medullated fibres which pass out of this ganglion by the gray rami communicating with the nerves forming the brachial plexus. The action of the nerve-fibres upon the sweat-glands cannot be explained as an indirect effect—for instance, as a result of a variation in the blood-flow. Experiments have repeatedly shown that, in the cat, stimulation of the sciatic still calls forth a secretion after the

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[1] *Archiv für die gesammte Physiologie*, 1875, Bd. xi. S. 71.
[2] *Journal of Physiology*, 1891, vol. xii. p. 347.

blood has been shut off from the leg by ligation of the aorta, or indeed after the leg has been amputated for as long as twenty minutes. So in human beings it is known that profuse sweating may often accompany a pallid skin, as in terror or nausea, while on the other hand the flushed skin of fever is characterized by the absence of perspiration. There seems to be no doubt at all that the sweat-nerves are genuine secretory fibres, producing the secretion directly by their action on the cells of the sweat-glands. In accordance with this physiological fact recent histological work has demonstrated that special nerve-fibres are supplied to the glandular epithelium. According to Arnstein [1] the terminal fibres form a small branching varicose ending in contact with the epithelial cells. The sweat-gland may be made to secrete in many ways other than by direct artificial excitation of the sweat-fibres; for example, by external heat, dyspnœa, muscular exercise, strong emotions, and by the action of various drugs such as pilocarpin, muscarin, strychnin, nicotin, picrotoxin, and physostigmin. In all such cases the effect is supposed to result from an action on the sweat-fibres, either directly on their terminations, or indirectly upon their cells of origin in the central nervous system. In ordinary life the usual cause of profuse sweating is a high external temperature or muscular exercise. With regard to the former it is known that the high temperature does not excite the sweat-glands immediately, but through the intervention of the central nervous system. If the nerves going to a limb be cut, exposure of that limb to a high temperature does not cause a secretion, showing that the temperature change alone is not sufficient to excite the gland or its terminal nerve-fibres. We must suppose, therefore, that the high temperature acts upon the sensory cutaneous nerves, possibly the heat-fibres, and reflexly stimulates the sweat-fibres. Although external temperature does not directly excite the glands, it should be stated that it affects their irritability either by direct action on the gland-cells or, as is more likely, upon the terminal nerve-fibres. At a sufficiently low temperature the cat's paw does not secrete at all, and the irritability of the glands is increased by a rise of temperature up to about 45° C.

Dyspnœa, muscular exercise, emotions, and many drugs affect the secretion, probably by action on the nerve-centres. Pilocarpin, on the contrary, is known to stimulate the endings of the nerve-fibres in the glands, while atropin has the opposite effect, completely paralyzing the secretory fibres.

Sweat-centres in the Central Nervous System.—The fact that secretion of sweat may be occasioned by stimulation of afferent nerves or by direct action upon the central nervous system, as in the case of dyspnœa, implies the existence of physiological centres controlling the secretory fibres. The precise location of the sweat-centre or centres has not, however, been satisfactorily determined. Histologically and anatomically the arrangement of the sweat-fibres resembles that of the vaso-constrictor fibres, and, reasoning from analogy, one might suppose the existence of a general sweat-centre in the medulla comparable to the vaso-constrictor centre, but positive evidence of the existence of such

[1] *Anatomischer Anzeiger*, 1895, Bd. x.

an arrangement is lacking. It has been shown than when the medulla is separated from the cord by a section in the cervical or thoracic region the action of dyspnœa, or of various sudorific drugs supposed to act on the central nervous system, may still cause a secretion. On the evidence of results of this character it is assumed that there are spinal sweat-centres, but whether these are few in number or represent simply the various nuclei of origin of the fibres to different regions is not definitely known. It is possible that in addition to these spinal centres there is a general regulating centre in the medulla.

Mammary Glands.

The mammary glands are undoubtedly epidermal structures comparable in development to the sweat- or the sebaceous glands. Whether they are to be homologized with the sweat- or with the sebaceous glands is not clearly determined. In most animals they are compound alveolar glands, and their acinous structure and the rich albuminous and fatty constituents of their secretion would seem to suggest a relationship to the sebaceous glands. But the histological structure of their alveoli with its single layer of epithelium points rather to a connection with the sweat-glands. Whatever may have been their exact origin in the primitive mammalia, there seems to be no question that they were derived in the first place from some of the ordinary skin-glands which at first simply opened on a definite area of the skin, but without a distinct mamma or nipple, as is seen now in the case of the monotremes. Later in the phylogenetic history of the gland the separate ducts united to form one or more larger ones, and these opened to the exterior upon the protrusion of the skin known as the nipple. The number and position of the glands vary much in the different mammalia. In man they are found in the thoracic region and are normally two in number. The milk-ducts do not unite to form a single canal, but form a group of fifteen to twenty separate systems, each of which opens separately upon the surface of the nipple. Before pregnancy the secreting alveoli are incompletely formed, but during pregnancy and at the time lactation begins the formation of the alveoli is greatly accelerated by proliferation of the epithelial cells.

Composition of the Secretion.—The general appearance and composition of the milk are well known. Microscopically milk consists of a liquid portion, or plasma, in which float an innumerable multitude of fine fat-droplets. The latter elements contain the milk-fat, which consists chiefly of neutral fats, stearin, palmitin, and olein, but contains also a small amount of the fats of butyric and caproic acid as well as slight traces of other fatty acid compounds and small amounts of lecithin, cholesterin, and a yellow pigment. Upon standing, a portion of these elements rises to the surface to form the cream. The milk-plasma holds in solution important proteid and carbohydrate compounds as well as the necessary inorganic salts. The proteids are casein, belonging to the group of nucleo-albumins; lactalbumin, which closely resembles the serum-albumin of blood, and lacto-globulin, which is similar to the paraglobulin of blood : the two latter proteids occur in much smaller quantities than the casein.

The chief carbohydrate in milk is the milk-sugar or lactose. Hammarsten[1] has succeeded in isolating from the mammary gland a nucleo-proteid containing a reducing group. He designates this substance as nucleo-glyco-proteid. It seems possible that a compound of this character might serve as the parent substance for both the casein and the lactose of the secretion. The mineral constituents are varied and, considered quantitatively, show an interesting relationship to the mineral composition of the body of the suckling (see p. 296). The fact that the inorganic salts of the milk vary so widely in quantitative composition from those of the blood has been used to show that they are not derived from the blood by the simple mechanical processes of filtration or dialysis, but are secreted by the epithelial cells of the gland. Traces of nitrogeneous excreta, such as urea, creatin, and creatinin, are also found in the milk-plasma, together with some lecithin and cholesterin and a small amount of citric acid occurring as citrate of calcium.

Histological Changes during Secretion.—The simple fact that substances are found in the milk which do not occur in the blood or lymph is sufficient proof that the epithelial cells are actively concerned in the process of secretion. Histological examination of the gland during lactation confirms fully this *a priori* deduction, and enables us to understand the probable origin of some of the important constituents.[2] In the resting gland during the period of gestation, or in certain alveoli during lactation, the alveoli are lined by a single layer of flattened or cuboidal cells, which have only a single nucleus, present a granular appearance, and have few or no fat-globules in them (Fig. 83). When such alveoli enter into the active formation of milk the epithelial cells increase in height, projecting in toward the lumen, the nuclei divide, and as a

FIG. 83.—Section through the middle of two alveoli of the mammary gland of the dog; condition of rest (after Heidenhain).

FIG. 84.—Mammary gland of dog, showing the formation of the secretion: *A*, medium condition of growth of the epithelial cells; *B*, a later condition (after Heidenhain).

rule (Steinhaus[3]) each cell contains two nuclei (Fig. 84). Fat-droplets develop in the cytoplasm, especially in the free end of the cell, and according to

[1] *Zeitschrift für physiologische Chemie*, 1894, Bd. xix. S. 19.
[2] See Heidenhain: *Hermann's Handbuch der Physiologie*, 1883, Bd. v. S. 381.
[3] *Du Bois-Reymond's Archiv für Physiologie*, 1892, Suppl. Bd., p. 54.

Steinhaus the nucleus nearest the lumen undergoes a fatty metamorphosis. According to the same author the granular material in the cytoplasm also undergoes a visible change; the granules, which in the resting cell are spherical, elongate during the stage of activity to threads that take on a spirochæta-like form. The acme of this phase of development is reached by the solution or disintegration of a portion of the end of the cell, the fragments being discharged into the lumen of the alveolus. The débris of this disintegrated portion of the cell helps to form the secretion; part of it goes into solution to form, probably, the albuminous and carbohydrate constituents, while the fat-droplets are set free to form the milk-fat. Apparently the basal portion of the cell regenerates its cytoplasm and thus continues to form new material for the secretion. In some cases, however, the whole cell seems to undergo dissolution, and its place is taken by a new cell formed by karyokinetic division of one of the neighboring epithelial cells. The origin of the peculiar colostrum corpuscles found in the milk during the first few days of its secretion has been explained differently by different observers. Heidenhain traces them to certain epithelial cells of the alveoli which at this time become rounded, develop numerous fat-droplets, and are finally discharged bodily into the lumen, although he was not able to actually trace the intermediate steps in the process. Steinhaus, on the contrary, thinks that these corpuscles are derived from the wandering cells of the connective tissue (*Mastzellen*) which at the beginning of lactation are very numerous, but seem to undergo fatty degeneration and elimination in the secretion of the newly active gland.

Control of the Secretion by the Nervous System.—There are indications that the secretion of the mammary glands is under the control, to some extent at least, of the central nervous system. For instance, in women during the period of lactation cases have been recorded in which the secretion was altered or perhaps entirely suppressed by strong emotions, by an epileptic attack, etc. This indication has not received satisfactory confirmation from the side of experimental physiology. Eckhard[1] found that section of the main nerve-trunk supplying the gland, the external spermatic, caused no difference in the quantity or quality of the secretion. Röhrig[2] obtained more positive results, inasmuch as he found that some of the branches of the external spermatic supply vaso-motor fibres to the blood-vessels of the gland and influence the secretion of milk by controlling the local blood-flow in the gland. Section of the inferior branch of this nerve, for example, gave increased secretion, while stimulation caused diminished secretion, as in the case of the vaso-constrictor fibres to the kidney. These results have not been confirmed by others—in fact, they have been subjected to adverse criticism—and they cannot, therefore, be accepted unhesitatingly.

Mironow[1] reports a number of interesting experiments made upon goats.

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[1] See Heidenhain: *Hermann's Handbuch der Physiologie*, Bd. v. Thl. 1. S. 392.

[2] *Virchow's Archiv für pathologische Anatomie*, etc., 1876, Bd. 67, S. 119.

[3] *Archives des Sciences biologiques*, St. Petersburg, 1894, vol. iii. p. 353.

He found that artificial stimulation of sensory nerves causes a diminution in the amount of secretion, thus confirming the opinion based upon observations upon the human being, that in some way the central nervous system exerts an influence on the mammary gland. When the mammary glands are completely isolated from their connections with the central nervous system, stimulation of an afferent nerve no longer influences the secretion. Mironow states also that although section of the external spermatic on one side does not influence the secretion, section of this nerve on both sides is followed by a marked diminution, and the same result is obtained when the gland on one side is completely isolated from all nervous connections. The diminution of the secretion in these cases comes on very slowly, after a number of days, so that the effect cannot be attributed to the removal of definite secretory fibres. Moreover, after apparently complete separation of the gland from all its extrinsic nerves, not only does the secretion, if it was previously present, continue to form although in less quantities, but in operations of this kind upon pregnant animals the glands increase in size during pregnancy and become functional after the act of parturition.

Experiments, therefore, as far as they have been carried, indicate that the gland is under the regulating control of the central nervous system, either through secretory or vaso-motor fibres, but that it is essentially an automatic organ. The bond of connection between it and the uterus seems to be, in part if not entirely, through the blood rather than through the nervous system. It should be added that Arnstein [1] has described a definite connection between the nerve-fibres and the epithelial cells of the gland. If this fact is corroborated it would amount to an histological proof of the existence of special secretory fibres, but the physiological evidence for the same fact is either negative or unsatisfactory.

Normal Secretion of the Milk.—As was said in speaking of the histology of the gland, the secreting alveoli are not fully formed until the first pregnancy. During the period of gestation the epithelial cells multiply, the alveoli are formed, and after parturition secretion begins. At first the secretion is not true milk, but a liquid differing in composition and known as the colostrum; this secretion is characterized microscopically by the existence of the colostrum corpuscles, which seem to be wandering cells that have undergone a complete fatty degeneration. After a few days the true milk is formed in the manner already described. According to Röhrig the secretion is continuous, but this statement needs confirmation. As the liquid is formed it accumulates in the enlarged galactophorous ducts, and after the tension has reached a certain point further secretion is apparently inhibited. If the ducts are emptied, by the infant or otherwise, a new secretion begins. The emptying of the ducts, in fact, seems to constitute the normal physiological stimulus to the gland-cells, but how this act affects the secreting cells, whether reflexly or directly, is not known. When the child is weaned the secretion under normal conditions soon ceases and the alveoli undergo retrograde changes, although

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[1] *Anatomischer Anzeiger*, 1895, Bd. x. S. 410.

they do not return completely to the condition they were in before the first pregnancy.

INTERNAL SECRETIONS.

According to the definition proposed on p. 152, the term internal secretion is here used to mean a specific substance or substances formed within a gland-ular organ and given off to the blood or lymph. As was said before, it is difficult to make a distinction between these internal secretions and the waste products of metabolism generally so far as method and place of formation and elimination are concerned. Every active tissue gives off waste products which are borne off in the lymph and blood, but as generally employed the term internal secretion is not meant to include all such products, but only the materials produced in distinctly glandular organs which are more or less specific to those organs, and which are supposed to have a general value to the body as a whole. The idea of an internal secretion seems to have been first advocated by Brown-Séquard in the course of some work upon extracts of the testis. Within the last few years the term has been frequently used, especially in connection with the valuable and interesting work done upon the pancreas and the so-called blood-vascular or ductless glands, the thyroids, adrenals, pituitary body, and spleen. In almost all cases our knowledge of the nature and importance of these internal secretions is in a formative stage; the literature, however, of the subject is already very great, and is increasing rapidly, while speculations are numerous, so that constant contact with current literature is necessary to keep pace with the advance in knowledge. In this section only an outline of the subject can be attempted.

Liver.—It has not been customary to speak of the liver as furnishing an internal secretion, but two of the products formed within this organ are so clearly known and their method of production is so typical of what is sup-posed to be the mechanism of internal secretion, that it is desirable both for the sake of convenience and consistency to include them under this general heading. Glycogen $(C_6H_{10}O_5)_n$ is formed within the liver-cells from the sugars and proteids brought to them in the blood of the portal vein, and in many cases the presence of this glycogen can be demonstrated microscopically within the cells. From time to time, however, the glycogen within the cell is converted into dextrose by a process of hydration,

$$C_6H_{10}O_5 + H_2O = C_6H_{12}O_6,$$

and the sugar so formed is by a secretory process of some kind given off to the blood to serve for the metabolism of the other tissues of the body, es-pecially the muscles. This elimination of its stored glycogen on the part of the liver may be regarded as a case of internal secretion. (For further details concerning glycogen, its properties and functions, see p. 266 and the section on Chemistry.) A second substance which is formed under the influence of the liver-cells and is then eliminated into the blood is urea. Urea constitutes the chief nitrogenous end-product of the metabolism of the proteid tissues; it

is eliminated from the body by the kidneys, but it is known not to be formed in these organs. Modern investigations (see p. 000) have seemed to show conclusively that this substance is formed mainly within the liver from some antecedent substance (carbamate of ammonia) which arises in the proteid tissues generally, but is not prepared for final elimination until in the liver or elsewhere it is converted into urea. Here again the liver-cells perform a metabolism for the good of the organism as a whole, and the act of passing out the urea into the blood may be regarded as an internal secretion. It is quite possible that in still other ways the liver-cells add to the blood elements of importance to the tissues of the body—as, for example, in the conservation and distribution of the iron of broken-down hæmoglobin (see p. 275), or in the synthetic combination of the products of putrefaction formed in the intestines (indol, skatol, phenol, etc.) with sulphuric acid (see p. 263); but concerning these matters our knowledge is not yet sufficiently definite to make positive statements.

Pancreas.—The importance of the external secretion, the pancreatic juice, of the pancreas has long been recognized, but it was not until 1889 that Von Mehring [1] and Minkowski proved that it furnishes also an equally important internal secretion. These observers succeeded in extirpating the entire pancreas without causing the immediate death of the animal, and found that in all cases this operation was followed by the appearance of sugar in the urine in considerable quantities. Further observations of their own and other experimenters have corroborated this result and added a number of interesting facts to our knowledge of this side of the activity of the pancreas. It has been shown that when the pancreas is completely removed a condition of glycosuria inevitably follows, even if carbohydrate food is excluded from the diet. Moreover, as in the similar pathological condition of glycosuria or diabetes mellitus in man there is an increase in the quantity of urine (polyuria), and of urea, and an abnormal thirst and hunger. These symptoms in cases of complete extirpation of the pancreas are followed by emaciation and muscular weakness, which finally end in death in about two weeks or less. If the pancreas is incompletely removed the glycosuria may be serious, or slight and transient, or absent altogether, depending upon the amount of pancreatic tissue left. According to the experiments of Von Mehring and Minkowski on dogs, a residue of one-fourth to one-fifth of the gland may be sufficient to prevent the appearance of sugar in the urine. The portion of pancreas left in the body may suffice to prevent glycosuria, partly or completely, even though its connection with the duodenum is entirely interrupted, thus indicating that the suppression of the pancreatic juice is not responsible for the glycosuria. The same fact is shown more conclusively by the following experiments: Glycosuria after complete removal of the pancreas from its normal connections may be prevented by grafting a portion of the pancreas elsewhere in the abdominal cavity or even under the skin. The ducts of the gland may be completely occluded by ligature or by injection of paraffin without seriously disturbing

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[1] *Archiv für exper. Pathologie und Pharmakologie*, 1890, Bd. xxvi. S. 371. See also Minkowski, *Ibid.*, 1893, Bd. xxxi. S. 85, for a more complete account.

the healthy condition of the animal. In the last experiment it is said that the normal secreting tubules of the gland undergo atrophy.

We must believe from these experiments that the pancreas produces a substance of some kind which is given off to the blood or lymph and which is either necessary for the normal consumption of sugar in the body, or else, as is held by some,[1] normally restrains the output of sugar from the liver and other sugar-producing tissues of the body. What this material is and how it acts has not yet been determined satisfactorily. It is interesting and suggestive to state in this connection that post-mortem examination in cases of diabetes mellitus in the human being has shown that this disease is associated in some instances with obvious alterations in the structure of the pancreas.

The Thyroid Body.—The thyroids are glandular structures found in all the vertebrates. In the mammalia they lie on either side of the trachea at its junction with the larynx. In man they are united across the front of the trachea by a narrow band or isthmus, and hence are sometimes spoken of as one structure, the thyroid body. In some of the lower mammals (*e. g.* dog) the isthmus is often absent. The thyroids in man are small bodies measuring about 50 millimeters in length by 30 millimeters in width; they have a distinct glandular structure but possess no ducts. Histological examination shows that they are composed of a number of closed vesicles varying in size. Each vesicle is lined by a single layer of cuboidal epithelium, while its interior is filled by a homogeneous glairy liquid, the colloid substance which is found also in the tissue between the vesicles lying in the lymph-spaces. This colloid substance is regarded as a secretion from the epithelial cells of the vesicles, and Biondi,[2] Langendorff,[3] and Hürthle[4] claim to have followed the development of the secretion in the epithelial cells by micro-chemical reactions. While the interpretation of the microscopical appearances given by these authors is not identical, they agree in believing that the colloid material is formed within some or all of the epithelial cells, and is eliminated into the lumen with or without a disintegration of the cell-substance. Moreover, Langendorff and Biondi believe that the colloid material is finally discharged into the lymphatics by the rupture of the vesicles. The composition of the colloid is incompletely known.

Parathyroids.—The parathyroids are a pair of small bodies lying lateral or posterior to the thyroids, and in some animals (rat) they are apparently contained within the substance of the thyroids. They are quite unlike the thyroids in structure, consisting of solid masses or columns of epithelial-like cells which are not arranged to form acinous vesicles. According to Schaper[5] these bodies are not always paired, but may have a multiple origin extending along the common carotid in the neighborhood of the thyroids. Experimental investigations seem to show that these bodies are probably immature structures

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[1] See Kaufmann : *Archives de Physiologie normale et pathologique*, 1895, p. 210.
[2] *Berliner Klinische Wochenschrift*, 1888.   [3] *Archiv für Physiologie*, 1889, Suppl. Bd.
[4] *Pflüger's Archiv für die gesammte Physiologie*, 1894, Bd. lvi. S. 1.
[5] *Archiv für mikroskopische Anatomie*, 1895, Bd. xlvi. S. 500.

which are capable of assuming the functions of the thyroids to a greater or less extent when these latter are removed or injured.

Accessory Thyroids.—In addition to the parathyroids a variable number of accessory thyroids have been described by different observers, occurring in the neck or even as far down as the heart. These bodies possess the structure of the thyroid, and presumably have the same function. After removal of the thyroids they may suffice to prevent a fatal result.

Functions of the Thyroids.—Very great interest has been excited within recent years with regard to the functions of the thyroids. In 1856 Schiff showed that in dogs complete extirpation of the two thyroids is followed by the death of the animal; and within the last few years similar results have been obtained by numerous observers. Death is preceded by a number of characteristic symptoms, such as muscular tremors, which may pass into spasms and convulsions, cachexia, emaciation and a more or less marked condition of apathy. The muscular phenomena seem to proceed from the central nervous system, since section of the motor nerves protects the muscles from the irritation. The metabolic changes may also be due primarily to an alteration in the condition of the cord and brain. Similar results have been obtained in cats. Among the herbivorous animals it was at first stated that removal of the thyroids does not cause death; but so far as the rabbit is concerned Gley[1] has shown that if care be taken to remove the parathyroids also, death is as certain and more rapid than in the case of the carnivora; and a similar result has been obtained upon rats by Christiani. It is still asserted, however, that in sheep, horses, and birds the glands may be removed without serious injury to the animal. Cases have been reported also in which dogs have recovered after complete thyroidectomy, but these cases are rare and may be explained probably by the presence of accessory thyroids which remain after the operation. It has been observed, too, that the operation is more rapidly and certainly fatal in young animals than in old ones. In the monkey as well as in man the evil results following the removal of the glands develop more slowly than in the lower animals, and give rise to a series of symptoms resembling those of myxœdema in man. Among these symptoms may be mentioned a pronounced anæmia, diminution of muscular strength, failure of the mental powers, abnormal dryness of the skin, loss of hairs, and a peculiar swelling of the subcutaneous connective tissue. Physiologists have shown that in the case of dogs the fatal results following thyroidectomy may be mitigated or entirely obviated by grafting a portion of the gland under the skin or in the peritoneal cavity. If the piece grafted is sufficiently large the animal recovers apparently completely from the operation. So also in removing the thyroids, if a small portion of the gland, or the parathyroids, be left undisturbed the fatal symptoms do not develop. In human beings suffering from myxœdema as the result of loss of function of the thyroids it has been abundantly shown that injections of ·thyroid extracts, or feeding the fresh gland, restores the individual to an approximately normal condition.

[1] *Archives de Physiologie normale et Pathologique*, 1892, p. 135.

It follows from these various observations that the thyroid glands play a very important part of some kind in the general metabolism of the body. Two views prevail as to the general nature of their function.[1] According to some the office of the thyroids is to remove some toxic substance which normally accumulates in the blood as the result of the body-metabolism. If the thyroids are extirpated this substance then increases in quantity and produces the observed symptoms by a process of auto-toxication. In support of this view there are numerous observations to show that the blood, or urine, or muscle-juice of thyroidectomized animals has a toxic effect upon sound animals. These latter results, however, do not appear to be marked or invariable, and in the hands of some experimenters have failed altogether. The second view is that the thyroids secrete a material, a true internal secretion, which after getting into the blood plays an important and indeed essential part in the metabolic changes of some or all of the organs of the body, but especially the central nervous system. In support of this view we have such facts as these: Injections of thyroid extracts have a beneficial and not an injurious influence; there is microscopic evidence to show that the epithelial cells participate actively in the formation of the colloid secretion and that this secretion eventually reaches the blood by way of the lymph-vessels; the beneficial material in the thyroid extracts may be obtained from the gland by methods which prove that it is a distinct and stable substance formed in the gland, as we might suppose would be the case if it formed part of a definite secretion. This latter fact, indeed, amounts to a proof that the important function of the thyroids is connected with a material secreted within its substance ; but it may still be questioned, perhaps, whether this material acts by antagonizing toxic substances produced elsewhere in the body or by directly influencing the body-metabolism. Much work has been done to isolate the beneficial material of the thyroid, particularly in relation to the therapeutic use of the gland in myxœdema and goitre. The mere fact that feeding the gland acts as well as injecting its extracts shows the resistant nature of the substance, since it is evidently not injured by the digestive secretions. It has been shown also by Baumann [2] that the gland material may be boiled for a long period with 10 per cent. sulphuric acid without destroying the beneficial substance. This observer has succeeded in isolating from the gland a substance to which the name thyroiodin is given, which is characterized by containing a relatively large percentage (9.3 per cent. of the dry weight) of iodine, and which preserves in large measure the beneficial influence of thyroid extracts in cases of myxœdema and parenchymatous goitre. This notable discovery shows that the thyroid tissue has the power of forming a specific organic compound of iodine, and and it is possible that its influence upon body-metabolism may be connected with this fact. In a later communication by Baumann and Roos [3] it is stated that the thyroiodin is contained within the gland mainly in a state of combi-

[1] See Schafer: "Address on Physiology," annual meeting of the British Medical Association, London, July–August, 1895.

[2] *Zeitschrift für physiologische Chemie*, 1896, Bd. xxi. S. 319.   [3] *Ibid.*, S. 481.

nation with proteid bodies, from which it may be separated by digestion with gastric juice or by boiling with acids. Most of the substance is combined with an albuminous proteid to which they give the name thyroiodalbumin, while a smaller part is united with a globulin-like proteid. In this paper still more favorable reports of the beneficial action of this substance are reported, and there can be but little doubt that the authors have succeeded in isolating the really effective substance of thyroid extracts. A future paper upon the chemical nature of thyroiodin is promised. Fränkel has also isolated a basic body —thyreo-antitoxin—to which he gives the formula $C_6H_{11}N_3O_5$, which also shows to some extent the beneficial effect of the thyroid extracts. Drechsel [1] has succeeded in isolating two crystalline basic bodies one of which is apparently identical with that described by Fränkel. Both of these bodies are said to have a beneficial influence when administered to thyroidectomized animals. Drechsel suggests that there may be three separate substances formed in the thyroid which are of value to the body, and that corresponding to these the thyroids may exert a threefold effect upon body-metabolism. Gourlay states that he has succeeded in proving the presence of a nucleo-albumin in the thyroids, and showing by microchemical reactions that this substance is present in the colloid secretion.

Adrenal Bodies.—The adrenal bodies—or, as they are frequently called in human anatomy, the suprarenal capsules—belong to the group of ductless glands. Their histology as well as their physiology is incompletely known. It was shown first by Brown-Séquard (1856) that removal of these bodies is followed rapidly by death. This result has been confirmed by many experimenters, and so far as the observations go the effect of complete removal is the same in all animals. The fatal effect is more rapid than in the case of removal of the thyroids, death following the operation usually in two to three days, or, according to some accounts, within a few hours. The symptoms preceding death are great prostration and muscular weakness, and marked diminution in vascular tone. These symptoms are said to resemble those occurring in Addison's disease in man, a disease which clinical evidence has shown to be associated with pathological lesions in the suprarenal capsules. It has been expected, therefore, that the results obtained for thyroid treatment of myxœdema might be repeated in cases of Addison's disease by the use of adrenal extracts. These expectations seem to have been realized in part, but complete and satisfactory reports are yet lacking. The physiology of the adrenals has usually been explained upon the auto-toxication theory. The death that comes after their removal has been accounted for upon the supposition that during life they remove or destroy a toxic substance produced elsewhere in the body, possibly in the muscular system. Oliver [2] and Schaefer, however, have recently given reasons for believing that this organ forms a peculiar substance which has a very definite physiological action especially upon the muscular system. They find that aqueous extracts of the medulla of the gland when injected into

[1] *Centralblatt für Physiologie*, 1896, Bd. ix., No. 24.
[2] *Journal of Physiology*, 1895, vol. xviii. p. 230.

the blood of a living animal have a remarkable influence upon the heart, blood-vessels, and skeletal muscles. The contractions of the latter are prolonged, somewhat as after the action of veratrin. Upon the blood-vessels the extracts cause a strong vascular contraction, giving an enormous increase in blood-pressure, and upon the heart muscles also, if the vagus nerves have been previously cut, there is a similar stimulating action manifested by an increase in the strength and frequency of the beats. These effects are obtained with very small doses of the extracts. Schaefer states that as little as 5½ milligrams of the dried gland may produce a maximal effect upon a dog weighing 10 kilograms. The effects produced by such extracts are quite temporary in character. In the course of a few minutes the blood-pressure returns to normal, as also the heart-beat, showing that the substance has been destroyed in some way in the body, although where or how this destruction occurs is not known. According to Schaefer the kidneys and the adrenals themselves are not responsible for this prompt elimination or destruction of the injurious substance. It is possible that the substance in question may be continually secreted under normal conditions by the adrenal bodies and play a very important part with reference to the functional activity of the muscular tissue.

Pituitary Body.—It is stated that complete removal of the pituitary body causes death, accompanied by symptoms which resemble somewhat those following thyroidectomy, such as muscular tremors and spasms, apathy, etc. A number of observers, therefore, have supposed that physiologically the pituitary body is related to the thyroids, and is able to vicariously assume, to a greater or less extent, the functions of the latter. The work upon this organ has not, however, made sufficient progress to enable any satisfactory statements to be made concerning its possible functional value.

Testis.—Some of the earliest work upon the effect of the internal secretions of the glands was done upon the reproductive glands, especially the testis, by Brown-Séquard.[1] According to this observer extracts of the fresh testis when injected under the skin or into the blood may have a remarkable influence upon the nervous system. The general mental and physical vigor and especially the activity of the spinal centres are greatly improved, not only in cases of general prostration and neurasthenia, but also in the case of the aged. Brown-Séquard maintained that this general dynamogenic effect is due to some unknown substance formed in the testis and subsequently passed into the blood, although he admitted that some of the same substance may be found in the external secretion of the testis, *i. e.* the spermatic liquid. More recently Poehl[2] asserts that he has prepared a substance, spermin, to which he gives the formula $C_5H_{14}N_2$, which has a very beneficial effect upon the metabolism of the body. He believes that this spermin is the substance which gives to the testicular extracts prepared by Brown-Séquard their stimulating effect. He claims for this substance an extraordinary action as a physiological tonic. The precise scientific value of the results of experiments with the

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[1] See *Archives de Physiologie normale et pathologique*, 1889-92.
[2] See *Zeitschrift für klinische Medicine* 1894, Bd. 26, S. 133.

testicular extracts cannot be estimated at present, in spite of the large litera-
ture upon the subject; we must wait for more detailed and exact experiments,
which doubtless will soon be made.   Quite recently Zoth[1] and also Pregel[2]
seem to have obtained exact objective proof, by means of ergographic records,
of the stimulating action of the testicular extracts upon the neuro-muscular
apparatus in man.   They find that injections of the testicular extracts cause not
only a diminution in the muscular and nervous fatigue resulting from muscu-
lar work, but also lessen the subjective fatigue sensations.   The fact that the
internal secretion of the testis, if it exists at all, is not absolutely essential to
the life of the body as a whole, as in the case of the thyroids, adrenals, and
pancreas, naturally makes the satisfactory determination of its existence and
action a more difficult task.

[1] *Pflüger's Archiv für die gesammte Physiologie*, 1896, Bd. 62, S. 335.   [2] *Ibid.*, S. 379.

IV. CHEMISTRY OF DIGESTION AND NUTRITION.

A. Definition and Composition of Foods; Nature of Enzymes.

Speaking broadly, what we eat and drink for the purpose of nourishing the body constitutes our food. A person in adult life who has reached his maximum growth, and whose weight remains practically constant from year to year, must eat and digest a certain average quantity of food daily to keep himself in a condition of health and to prevent loss of weight. In such a case we may say that the food is utilized to repair the wastes of the body —that is, the destruction of body-material which goes on at all times, even during sleep, but which is increased by the physical and psychical activities of the waking hours—and in addition it serves as the source of heat, mechanical work, and other forms of energy liberated in the body. In a person who is growing—one who is, as we say, laying on flesh or increasing in stature—a certain portion of the food is used to furnish the energy and to cover the wastes of the body, while a part is converted into the new tissues formed during growth. The material that we eat or drink as food is for the most part in an insoluble form, and, moreover, it has a composition differing oftentimes very widely from that of the tissues which it is intended to form or to repair. The object of the processes of digestion carried on in the alimentary tract is to change this food so that it may be absorbed into the blood, and at the same time so to alter its composition that it can be utilized by the tissues of the body. For we shall find, later on, that certain foods—eggs, for example—which are very nutritious when taken into the alimentary canal and digested cannot be used at all by the tissues if injected at once, unchanged, into the blood. The food of mankind is most varied in character. At different times of the year and in different parts of the world the diet is changed to suit the necessities of the occasion. When, however, we come to analyze the various animal and vegetable foods made use of by mankind, it is found that they are all composed of one or more of five or six different classes of substances to which the name *food-stuffs* or alimentary principles has been given. To ascertain the nutritive value of any food, it must be analyzed and the percentage amounts of the different food-stuffs contained in it must be determined. The classification of food-stuffs usually given is as follows:

Food-stuffs.
{
Water;
Inorganic salts;
Proteids (or proteid-containing bodies);
Albuminoids (a group of bodies resembling proteids, but having in some respects a different nutritive value);
Carbohydrates;
Fats.
}

What is known with regard to the specific nutritive value of each of these substances will be given later on, after the processes of digestion have been described. A few general remarks, however, at this place will serve to give the proper standpoint from which to begin the study of the chemistry of digestion and nutrition.

Water and Salts.—Water and salts we do not commonly consider as foods, but the results of scientific investigation, as well as the experience of life, show that these substances are absolutely necessary to the body. The tissues must maintain a certain composition in water and salts in order to function normally, and, since there is a continual loss of these substances in the various excreta, they must continually be replaced in some way in the food. It is to be borne in mind in this connection that water and salts constitute a part of all our solid foods, so that the body gets a partial supply at least of these substances in everything we eat.

Proteids.—The composition and different classes of proteids are described from a chemical standpoint in the section on The Chemistry of the Body. Different varieties of proteids are found in animal as well as in vegetable foods. The chemical composition in all cases, however, is approximately the same. Physiologically, they are supposed to have equal nutritive values outside of differences in digestibility, a detail which will be given later. The essential use of the proteids to the body is that they supply the material from which the new proteid tissue is made or the old proteid tissue is repaired, although, as we shall find when we come to discuss the subject more thoroughly (p. 285), proteids are also extremely valuable as sources of energy to the body. Inasmuch as the most important constituent of living matter is the proteid part of its molecule, it will be seen at once that proteid food is an absolute necessity. Proteids contain nitrogen, and they are frequently spoken of as the *nitrogenous* foods; carbohydrates and fats, on the contrary, do not contain nitrogen. It follows immediately from this fact that fats and carbohydrates alone could not suffice to make new protoplasm. If our diet contained no proteids, the tissues of the body would gradually waste away and death from starvation would result. All the food-stuffs are necessary in one way or another to the preservation of perfect health, but proteids, together with a certain proportion of water and inorganic salts, are absolutely necessary for the bare maintenance of animal life—that is, for the formation and preservation of living protoplasm. Whatever else is contained in our food, proteid of some kind must form a part of our diet. The use of

the other food-stuffs is, as we shall see, more or less accessory. It may be worth while to recall here the familiar fact that in respect to the nutritive importance of proteids there is a wide difference between animal and vegetable life. What is said above applies, of course, only to animals. Plants can, and for the most part do, build up their living protoplasm upon diets containing no proteid. With some exceptions which need not be mentioned here, the food-stuffs of the great group of chlorophyll-containing plants, outside of oxygen, consist of water, CO_2, and salts, the nitrogen being found in the last-mentioned constituent.

Albuminoids.—Gelatin, such as is found in soups or is used in the form of table-gelatin, is a familiar example of the albuminoids. They are not found to any important extent in our raw foods, and they do not therefore usually appear in the analyses given of the composition of foods. An examination of the composition and properties of these bodies (see section on The Chemistry of the Body) shows that they resemble closely the proteids. Unlike the fats and carbohydrates, they contain nitrogen, and they are evidently of complex structure. Nevertheless, they cannot be used in place of proteids to build protoplasm. They are important foods without doubt, but their value is similar in a general way to that of the non-nitrogenous foods, fats and carbohydrates, rather than to the so-called "nitrogenous foods," the proteids.

Carbohydrates.—We include among carbohydrates the starches, sugars, gums, and the like (see Chemical section); they contain no nitrogen. Their physiological value lies in the fact that they are destroyed in the body and a certain amount of energy is thereby liberated. The energy of muscular work and of the heat of the body comes largely from the destruction or oxidation of carbohydrates. Inasmuch as we are continually giving off energy from the body, chiefly in the form of muscular work and heat, it follows that material for the production of this energy must be taken in the food. Carbohydrates form perhaps the easiest and cheapest source of this energy. They constitute the bulk of our ordinary diet.

Fats.—In the group of fats we include not only what is ordinarily understood by the term, but also the oils, animal and vegetable, which form such a common part of our food. Fats contain no nitrogen (see Chemical section). Their use in the body is substantially the same as that of the carbohydrates. Weight for weight, they are more valuable than the carbohydrates as sources of energy, but the latter are cheaper, more easily digested, and more easily destroyed in the body. For these reasons we find that under most conditions fats are a subsidiary article of food as compared with the carbohydrates. From the standpoint of the physiologist, fats are of special interest because the animal body stores up its reserve of food material mainly in that form. The history of the origin of the fats of the body is one of the most interesting parts of the subject of nutrition, and it will be discussed at some length in its proper place.

As has been said, our ordinary foods are mixtures of some or all of the food-stuffs, together with such things as flavors or condiments, whose nutritive

value is of a special character. Careful analyses have been made of the different articles of food, mostly of the raw or uncooked foods. As might be expected, the analyses on record differ more or less in the percentages assigned to the various constituents, but almost any of the tables published give a just idea of the fundamental nutritive value of the common foods. For details of separate analyses reference may be made to some of the larger works upon the composition of foods.[1] The subjoined table is one compiled by Munk from the analyses given by König:

Composition of Foods.

In 100 parts.	Water.	Proteid.	Fat.	Carbohydrate.		Ash.
				Digestible.	Cellulose.	
Meat	76.7	20.8	1.5	0.3	. . .	1.3
Eggs	73.7	12.6	12.1	. . .	. . .	1.1
Cheese	36–60	25–33	7–30	3–7	. . .	3–4
Cow's milk	87.7	3.4	3.2	4.8	. . .	0.7
Human milk	89.7	2.0	3.1	5.0	. . .	0.2
Wheat flour	13.3	10.2	0.9	74.8	0.3	0.5
Wheat bread	35.6	7.1	0.2	55.5	0.3	1.1
Rye flour	13.7	11.5	2.1	69.7	1.6	1.4
Rye bread	42.3	6.1	0.4	49.2	0.5	1.5
Rice	13.1	7.0	0.9	77.4	0.6	1.0
Corn	13.1	9.9	4.6	68.4	2.5	1.5
Macaroni	10.1	9.0	0.3	79.0	0.3	0.5
Peas, beans, lentils	12–15	23–26	1½–2	49–54	4–7	2–3
Potatoes	75.5	2.0	0.2	20.6	0.7	1.0
Carrots	87.1	1.0	0.2	9.3	1.4	0.9
Cabbages	90	2–3	0.5	4–6	1–2	1.3
Mushrooms	73–91	4–8	· 0.5	3–12	1–5	1.2
Fruit	84	0.5	. . .	10 ·	4	0.5

An examination of this table will show that the animal foods, particularly the meats, are characterized by their small percentage in carbohydrate and by a relatively large amount of proteid or of proteid and fat. With regard to the last two food-stuffs, meats differ very much among themselves. Some idea of the limits of variation may be obtained from the following table, taken chiefly from König's analyses:

	Water.	Proteid.	Fat.	Carbohydrate.	Ash.
Beef, moderately fat	73.03	20.96	5.41	0.46	1.14
Veal, fat	72.31	18.88	7.41	0.07	1.33
Mutton, moderately fat	75.99	17.11	5.77	. . .	1.33
Pork, lean	72.57	20.05	6.81	. . .	1.10
Ham, salted	62.58	22.32	8.68	. . .	6.42
Pork (bacon), very fat [2]	10.00	3.00	80.50	. . .	6.5
Mackerel [2]	71.6	18.8	8.2	. . .	1.4

The vegetable foods are distinguished, as a rule, by their large percentage in carbohydrates and the relatively small amounts of proteids and fats, as seen, for example, in the composition of rice, corn, wheat, and potatoes. Neverthe-

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[1] König, *Die Menschlichen Nahrungs und Genussmittel*, 3d ed., 1889; Parke's *Manual of Practical Hygiene*, section on Food.

[2] Atwater: *The Chemistry of Foods and Nutrition*, 1887.

less, it will be noticed that the proportion of proteid in some of the vegetables is not at all insignificant. They are characterized by their excess in carbohydrates rather than by a deficiency in proteids. The composition of peas and other leguminous foods is remarkable for the large percentage of proteid, which exceeds that found in meats. Analyses such as are given here are indispensable in determining the true nutritive value of foods. Nevertheless, it must be borne in mind that the chemical composition of a food is not alone sufficient to determine its precise value in nutrition. It is obviously true that it is not what we eat, but what we digest and absorb, that is nutritious to the body, so that, in addition to determining the proportion of food-stuffs in any given food, it is necessary to determine to what extent the several constituents are digested. This factor can be obtained only by actual experiments; a number of results bearing upon this point have been collected which will be spoken of later. It may be said here, however, that in general the proteids of animal foods are more completely digestible than are those of vegetables, and with them, therefore, chemical analysis comes nearer to expressing directly the nutritive value.

The physiology of digestion consists chiefly in the study of the chemical changes which the food undergoes during its passage through the alimentary canal. It happens that these chemical changes are of a peculiar character. The peculiarity is due to the fact that the changes of digestion are effected through the agency of a group of bodies known as *enzymes*, or unorganized ferments, whose chemical action is different from that of the ordinary reagents with which we have to deal. It will save useless repetition to give here certain general facts that are known with reference to these bodies, reserving for future treatment the details of the action of the specific enzymes found in the different digestive secretions.

Enzymes.—Enzymes, or unorganized ferments, or unformed ferments, is the name given to a group of bodies produced in animals and plants, but not themselves endowed with the structure of living matter. The term *unorganized* or *unformed* ferment was formerly used to emphasize the distinction between these bodies and living ferments, such as the yeast-plant or the bacteria. "Enzyme," however, is a better name, and is coming into general use. Enzymes are to be regarded as dead matter, although produced in living protoplasm. Chemically, they are defined as complex organic compounds containing nitrogen. Their exact composition is unknown, as it has not been found possible heretofore to obtain them in pure enough condition for analysis. Although several elementary analyses are recorded, they cannot be considered reliable. It is not known whether or not the enzymes belong to the group of proteids. Solutions of most of the enzymes give some or all of the general reactions for proteids, but there is always an uncertainty as to the purity of the solutions. With reference to the fibrin ferment of blood, one of the enzymes, observations have recently been made which seem to show that it at least belongs to the group of combined proteids, nucleo-albumins (for details see the section on Blood). But even should this be true, we are

not justified in making any general application of this fact to the whole group.

Classification of Enzymes.—Enzymes are classified according to the kind of reaction they produce—namely:

1. *Proteolytic enzymes*, or those acting upon proteids, converting them to a soluble modification, peptone or proteose. As examples of this group we have in the animal body *pepsin* of the gastric juice and *trypsin* of the pancreatic juice. In plants a similar enzyme is found in the pineapple family (bromelin) and in the papaw (papaïn).

2. *Amylolytic enzymes*, or those acting upon the starches, converting them to a soluble form, sugar, or sugar and dextrin. As examples of this group we have in the animal body *ptyalin*, found in saliva, *amylopsin*, found in pancreatic juice, and in the liver an enzyme capable of converting glycogen to sugar. In the plants the best-known example is *diastase*, found in germinating seeds. This particular enzyme has been known for a long time from the use made of it in the manufacture of beer. In fact, the name "diastase" is frequently used in a generic sense, "the diastatic enzymes," to characterize the entire group of starch-destroying ferments.

3. *Fat-splitting enzymes*, or those acting upon the neutral fats, breaking them up into glycerin and the corresponding fatty acid. The best-known example in the animal body is found in the pancreatic secretion; it is known usually as *steapsin*, although it has been given several names. Similar enzymes are known to occur in a number of seeds.

4. *Inverting enzymes*, or those having the property of converting the double into the single sugars—the di-saccharides, such as *cane-sugar* and *maltose*, into the mono-saccharides, such as *dextrose* and *levulose*. Two enzymes of this character have been found in the animal body, one acting upon cane-sugar and one on maltose. They are usually spoken of as *invertin* or inverting enzymes. A similar enzyme may be obtained from the yeast-plant.

5. *Coagulating enzymes*, or those acting upon soluble proteids, precipitating them in an insoluble form. As examples of this class we have fibrin ferment (*thrombin*), formed in shed blood, and *rennin*, the milk-curdling ferment of the gastric juice. An enzyme similar to rennin has been found in pineapple-juice.

These five classes comprise the groups of enzymes that are known to occur in the animal body. One or more examples of each group take part in the digestion of food at some time during its passage through the alimentary canal. Two other important groups of enzymes which are not formed in the animal body may be mentioned briefly in this connection for the sake of completeness:

6. *Glucoside-splitting enzymes*, or those acting upon the glucosides, giving a carbohydrate as one of the products of decomposition. Examples: *emulsin*, found in bitter almonds; *myrosin*, in mustard-seeds.

7. *Urea-splitting enzymes*, or those acting upon urea, converting it to *ammonium carbonate;* found in many bacteria, especially in those normally occurring in the urine.

A great number of general reactions have been discovered, applicable, with

an exception here and there, to the whole group of enzymes. Among these reactions the following are the most useful or significant:

1. *Solubility.*—The enzymes are all soluble in water. They are also soluble in glycerin, this being the most generally useful solvent for obtaining extracts of the enzymes from the organs in which they are formed.

2. *Effect of Temperature.*—In a moist condition they are all destroyed by temperatures below the boiling-point; 60° to 80° C. are the limits actually observed. Very low temperatures retard or even suspend entirely (0° C.) their action, without, however, destroying the enzyme. For each enzyme there is a temperature at which its action is greatest.

3. *Incompleteness of Action.*—With the exception perhaps of the coagulating enzymes, they are characterized by the fact that in any given solution they never completely destroy the substance upon which they act. It seems that the products of their activity, as they accumulate, finally prevent the enzymes from acting further; when these products are removed the action of the enzyme begins again. The most familiar example of this very striking peculiarity is found in the action of pepsin on proteids. The products of digestion in this case are peptones and proteoses, and when they have reached a certain concentration they prevent any further proteolysis on the part of the pepsin.

4. *Relation of the Amount of Enzyme to the Effect it Produces.*—With most substances the extent of the chemical change produced is proportional to the amount of the substance entering into the reaction. With the enzymes this is not so. Except for very small quantities, it may be said that the amount of change caused is independent of the amount of enzyme present, or, to state the matter more accurately, " with increasing amounts of enzymes the extent of action also increases, reaching a maximum with a certain percentage of enzyme; increase of enzyme beyond this has no effect."[1] This fact was formerly interpreted to mean that the enzyme is not used up—that is, not permanently altered —by the reaction which it causes. This belief, indeed, must be true substantially, but it has been found practically that a given solution of enzyme cannot be used over and over again indefinitely. It is generally believed now that, although an enzyme causes an amount of change in the substance it acts upon altogether out of proportion to the amount of its own substance, nevertheless it is eventually destroyed; its action is not unlimited. Whether this using up of the enzyme is a necessary result of its activity, or is, as it were, an accidental effect from spontaneous changes in its own molecule, remains undetermined.

Theories of the Manner of Action of the Enzymes.—It is now known that with the possible exception of the coagulating enzymes the action of the enzymes is that of hydrating agents; they produce their effect by what is known as *hydrolysis;* that is, they cause the molecules of the substance upon which they act to take up one or more molecules of water; the resulting molecule then splits or is dissociated, with the formation of two or more simpler bodies. This is one of the most significant facts in connection with the

[1] Tammann: *Zeitschrift für physiologische Chemie,* xvi., 1892, p. 271.

action of the enzymes; it is well illustrated by the action of invertin on cane-sugar, as follows:

$$C_{12}H_{22}O_{11} + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6$$

<div align="center">Cane-sugar.   Dextrose.   Levulose.</div>
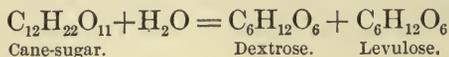
In what way enzymes cause the substances they act upon to take up water is unknown. The fact that they are not themselves used up in the reaction proportionally to the change they cause formerly influenced physiologists and chemists to explain their effect as due to *catalysis*, or contact action. In its original sense this designation meant that the molecules of enzyme act by their mere presence or contiguity, but it need scarcely be said that a statement of this kind does not amount to an explanation of their manner of action; to say they "act by catalysis" means nothing in itself. Efforts to explain their action have resulted in a number of hypotheses, a detailed account of which would hardly be appropriate here. It may be mentioned that two ideas have found most general acceptance: one, that the vibrations of the molecules of enzyme set into more rapid vibration the molecules of the substance acted upon, thus leading to the taking up of water and to the subsequent splitting; the other idea is that the enzyme enters into a definite chemical reaction, in which, however, it plays the part of a carrier or go-between, so that, although the enzyme is directly concerned in producing a chemical change, the final outcome is that it remains in its original condition. A number of chemical reactions of this general character are known, in which some one substance passes through a cycle of changes, aiding in the production of new compounds, but itself returning always to its first condition; for example, the part taken by H_2SO_4 in the manufacture of ether from alcohol, or the successive changes of hæmoglobin to oxyhæmoglobin and back again to hæmoglobin after giving up its oxygen to the tissues. Perhaps the most suggestive reaction of this character is the one quoted by Chittenden [1] to illustrate this very hypothesis as to the manner of action of enzymes, as follows: Oxygen and carbon monoxide gas, if perfectly dry, will not react upon the passage of an electric spark. If, however, a little aqueous vapor is present, they may be made to unite readily, with the formation of CO_2. The water in this case, without doubt, enters into the reaction, but in the end it is re-formed, and the final result is as though the water had not directly participated in the process. The reactions supposed to take place are explained by the following equations:

$$CO + 2H_2O + O_2 = CO(OH)_2 + H_2O_2.$$
$$H_2O_2 + CO = CO(OH)_2.$$
$$2CO(OH)_2 = 2CO_2 + 2H_2O.$$
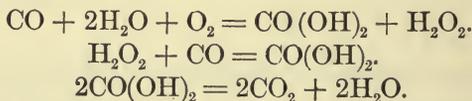
B. SALIVARY DIGESTION.

The first of the digestive secretions with which the food comes into contact is *saliva*. This liquid is a mixed secretion from the six large salivary glands (parotids, submaxillaries, and sublinguals) and the smaller mucous and serous

[1] Cartwright Lectures, *Medical Record*, New York, April 7, 1894.

glands which open into the mouth. The physiological anatomy of these glands and the mechanism by which the secretions are produced and regulated will be found described fully in the section on Secretion; we are concerned here only with the composition of the secretion after it is formed, and with its action upon foods.

Properties and Composition of the Mixed Saliva.—Filtered saliva is a clear, viscid, transparent liquid. As obtained usually from the mouth, it is more or less turbid, owing to the presence in it, in suspension, of particles of food or of detached cells from the epithelium of the mouth. A somewhat characteristic cell contained in it in small numbers is the so-called "salivary corpuscle." These bodies are probably leucocytes, altered in structure, which have escaped into the secretion. So far as is known, they have no physiological value. The specific gravity of the mixed secretion is on an average 1003, and its reaction is normally alkaline. The total amount of secretion during twenty-four hours varies naturally with the individual and the conditions of life; the estimates made vary from 300 to 1500 grams. Chemically, in addition to the water, the saliva contains mucin, ptyalin, albumin, and inorganic salts. The proportions of these constituents are given in the following analysis (Hammerbacher):

		In 1000 parts.
Water	. . . .	994.203
Solids:		
Mucin (and epithelial cells)	2.202	
Ptyalin and albumin	1.390	5.797
Inorganic salts	2.205	
Potassium sulphocyanide	0.041	

The inorganic salts, in addition to the sulphocyanide, which occurs only in traces, consist of the chlorides of potassium and sodium, the sulphate of potassium, and the phosphates of potassium, sodium, calcium, and magnesium; the earthy phosphates form about 9.6 per cent. of the total ash. *Mucin* is an important constituent of saliva; it gives to the secretion its ropy, viscid character, which is of so much value in the mechanical function it fulfils in swallowing. This substance is formed in the salivary glands. Its formation in the protoplasm of the cells may be followed microscopically (see the section on Secretion). Chemically, it is now known to be a combination of a proteid with a carbohydrate group (see section on The Chemistry of the Body). So far as known, mucin has no function other than its mechanical use. The presence of potassium sulphocyanide (KCNS) among the salts of saliva has always been considered interesting, since, although it occurs normally in urine as well as in saliva, it is not a salt found commonly in the secretions of the body, and its occurrence in saliva seemed to indicate some special activity on the part of the salivary gland, the possible value of which has been a subject of speculation. In the saliva, however, the sulphocyanide is found in such minute traces and its presence is so inconstant that no special functional importance can be attributed to it. It is supposed to be derived from the decomposition of proteids, and it represents, therefore, one of the end-products of proteid metab-

olism. Potassium sulphocyanide may be detected in saliva by adding to the latter a dilute acidulated solution of ferric chloride, a reddish color being produced.

Ptyalin and its Action.—From a physiological standpoint the most important constituent of saliva is *ptyalin*. It is an unorganized ferment or enzyme belonging to the amylolytic or diastatic group (p. 218) and possessing the general properties of enzymes already enumerated. It is found in human saliva and in that of many of the lower animals—for example, the pig and the herbivora—but it is said to be absent in the carnivora. Ptyalin has not been isolated in a sufficiently pure condition for satisfactory analysis, so that its chemical nature is undetermined; we depend for its detection upon its specific action—that is, its effect upon starch. Speaking roughly, we say that ptyalin converts starch into sugar, but when we come to consider the details of its action we find that it is complicated and that it consists in a series of hydrolytic splittings of the starch molecule; the exact products of the reaction depend upon the stage at which the action is interrupted. To demonstrate the action of ptyalin on starch it is only necessary to make a suitable starch paste by boiling some powdered starch in water, and then to add a little fresh saliva. If the mixture is kept at a proper temperature (30° to 40° C.), the presence of sugar may be detected within a few minutes. The sugar that is formed was for a time supposed to be ordinary grape-sugar (dextrose, $C_6H_{12}O_6$), but later experiments have shown conclusively that it is maltose ($C_{12}H_{22}O_{11}$-H_2O), a form of sugar more closely related in formula to cane-sugar (see Chemical section). In experiments of the kind just described two facts may easily be noticed: first, that the conversion of starch to sugar is not direct, but occurs through a number of intermediate stages; second, that the starch is not entirely converted to sugar under the conditions of such experiments—namely, when the digestion is carried on in a vessel, digestion *in vitro*. The second fact is an illustration of the incompleteness of action of the enzymes, a general property which has already been noticed. We may suppose, in this as in other cases, that the products of digestion, as they accumulate in the vessel, tend to retard and finally to suspend the amylolytic action of the ptyalin. In normal digestion, however, it is usually the case that the products of digestion, as they are formed, are removed by absorption, and if the above explanation of the cause of the incompleteness of action is correct, then under normal conditions we should expect a complete conversion of starch to sugar. Lea[1] states that if the products of ptyalin action are partially removed by dialysis during digestion *in vitro*, a much larger percentage of maltose is formed. His experiments would seem to indicate that in the body the action of the amylolytic ferments may be complete, and that the final product of their action may be maltose alone. It will be found that this statement applies practically not to the ptyalin, but to the similar amylolytic enzyme in the pancreatic secretion, owing to the fact that, normally, food is held in the mouth for a short time only, and

[1] *Journal of Physiology*, vol. xi., 1890, p. 227.

that ptyalin digestion is soon interrupted after the food reaches the stomach. With reference to the intermediate stages or products in the conversion of starch to sugar it is difficult to give a perfectly clear account. It was formerly thought that the starch was first converted to dextrin, and this in turn was converted to sugar. It is now believed that the starch molecule, which is quite complex, consisting of some multiple of $C_6H_{10}O_5$—possibly $(C_6H_{10}O_5)_{20}$—first takes up water, thereby becoming soluble (soluble starch, amylodextrin), and then splits, with the formation of dextrin and maltose, and that the dextrin again undergoes the same hydrolytic process, with the formation of a second dextrin and more maltose; this process may continue under favorable conditions until only maltose is present. The difficulty at present is in isolating the different forms of dextrin that are produced. It is usually said that at least two forms occur, one of which gives a red color with iodine, and is therefore known as *erythrodextrin*, while the other gives no color reaction with iodine, and is termed *achroödextrin*. It is pretty certain, however, that there are several forms of achroödextrin, and, according to some observers, erythrodextrin also is really a mixture of dextrins with maltose in varying proportions. In accordance with the general outline of the process given above, Neumeister[1] proposes the following schema, which is useful because it gives a clear representation of one theory, but which must not be considered as satisfactorily demonstrated (see also the section on Chemistry of the Body).

Starch—soluble starch (amylodextrin).
⟨ Maltose.
Erythrodextrin.
⟨ Maltose.
Achroödextrin α.
⟨ Maltose.
Achroödextrin β.
⟨ Maltose.
Achroödextrin γ (maltodextrin).
⟨ Maltose.
Maltose.
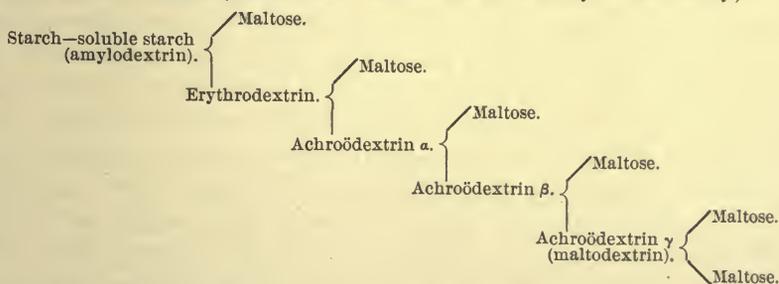
This schema represents the possibility of an ultimate conversion of all the starch into maltose, and it shows at the same time that maltose may be present very early in the reaction, and that it may occur together with one or more dextrins, according to the stage of the digestion. It should be said in conclusion that this description of the manner of action of the ptyalin is supposed to apply equally well to the amylolytic enzyme of the pancreatic secretion, the two being, so far as known, identical in their properties. From the standpoint of relative physiological importance the description of the details of amylolytic digestion should have been left until the functions of the pancreatic juice were considered. It is introduced here because, in the natural order of treatment, ptyalin is the first of this group of ferments to be encountered. It is interesting also to remember in this connection that starch can be converted into sugar by a process of hydrolytic cleavage by boiling with dilute mineral acids. Although the general action of dilute acids and of amylolytic

[1] *Lehrbuch der physiologischen Chemie*, 1893, p. 232.

enzymes is similar, the two processes are not identical, since in the first process dextrose is the sugar formed, while in the second it is maltose. Moreover, variations in temperature affect the two reactions differently.

Conditions Influencing the Action of Ptyalin.—*Temperature.*—As in the case of the other enzymes, ptyalin is very susceptible to changes of temperature. At 0° C. its activity is said to be suspended entirely. The intensity of its action increases with increase of temperature from this point, and reaches its maximum at about 40° C. If the temperature is raised much beyond this point, the action of the ptyalin decreases, and at from 65° to 70° C. the enzyme is destroyed. In these latter points ptyalin differs from diastase, the enzyme of malt. Diastase shows a maximum action at 50° C. and is destroyed at 80° C.

Effect of Reaction.—The normal reaction of saliva is slightly alkaline. Chittenden[1] has shown, however, that ptyalin acts as well, or even better, in a perfectly neutral medium. A strong alkaline reaction retards or prevents its action. The most marked influence is exerted by acids. Free hydrochloric acid to the extent of only 0.003 per cent. (Chittenden) is sufficient to practically stop the amylolytic action of enzyme, and a slight increase in acidity not only stops the action, but also destroys the enzyme. The latter fact is of practical importance because it indicates that the action of ptyalin on starch must be suspended after the food reaches the stomach.

Condition of the Starch.—It is a well-known fact that the conversion of starch to sugar by enzymes takes place much more rapidly with cooked starch—for example, starch paste. In the latter condition sugar begins to appear in a few minutes (one to four), provided a good enzyme solution is used. With starch in a raw condition, on the contrary, it may be many minutes, or even several hours, before sugar can be detected. The longer time required for raw starch is partly explained by the well-known fact that the starch-grains are surrounded by a layer of cellulose or cellulose-like material which resists the action of ptyalin. When boiled, this layer breaks and the starch in the interior becomes exposed. In addition, the starch itself is changed during the boiling; it takes up water, and in this hydrated condition is acted upon more rapidly by the ptyalin. The practical value of cooking vegetable foods is evident from these statements without further comment.

Physiological Value of Saliva.—Although human saliva contains ptyalin, and this enzyme is known to possess very energetic amylolytic properties, yet it is probable that it has an insignificant action in normal digestion. The time that food remains in the mouth is altogether too short to suppose that the starch is profoundly affected by the ptyalin. It would seem that whatever change takes place must be confined to the initial stages. After the mixed saliva and food are swallowed the acid reaction of the gastric juice soon stops completely all further amylolytic action. The complete digestion of the carbohydrates takes place after the food (chyme) has reached the small intestine, under the influence of the amylopsin of the pancreatic secretion. For these reasons it is

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[1] *Studies from the Laboratory of Physiological Chemistry of Yale College,* vol. i., 1884.

usually believed that the main value of the saliva, to the human being and to the carnivora at least, is that it facilitates the swallowing of food. It is impossible to swallow perfectly dry food. The saliva, by moistening the food, not only enables the swallowing act to take place, but its viscous consistency must aid also in the easy passage of the food along the œsophagus. Among the herbivora it is probable that the longer retention of food in the mouth gives the saliva opportunity for more complete digestive action.

C. Gastric Digestion.

After the food reaches the stomach it is exposed to the action of the secretion of the gastric mucous membrane, known usually as the *gastric juice*. The physiological mechanisms involved in the production and regulation of this secretion, and the important part played in gastric digestion by the movements of the stomach, will be found described in other sections (Secretion, Movements of Alimentary Canal). It is sufficient here to say that the secretion of gastric juice begins with the entrance of food into the stomach. By means of the muscles of the stomach the contained food is kept in motion for several hours and is thoroughly mixed with the gastric secretion, which during this time is exerting its digestive action upon certain of the food-stuffs. From time to time portions of the liquefied contents, known as *chyme*, are forced into the duodenum, and their digestion is completed in the small intestine. Gastric digestion and intestinal digestion go more or less hand in hand, and usually it is impossible to tell in any given case just how much of the food will undergo digestion in the stomach and how much will be left to the action of the intestinal secretions. It is possible, however, to collect the gastric secretion or to make an artificial juice and to test its action upon food-stuffs by digestions *in vitro*. Much of our fundamental knowledge of the digestive action of the gastric juice has been obtained in this way, although this has been supplemented, of course, by numerous experiments upon lower animals and human beings.

Methods of Obtaining Normal Gastric Juice.—The older methods used for obtaining normal gastric juice were very unsatisfactory. For instance, an animal was made to swallow a clean sponge to which a string was attached so that the sponge could afterward be removed and its contents be squeezed out ; or there was given the animal to eat some indigestible material, to start the secretion of juice by mechanical stimulation, the animal being killed at the proper time and the contents of its stomach being collected. A better method of obtaining normal juice was suggested by the famous observations of Beaumont[1] upon Alexis St. Martin. St. Martin, by the premature discharge of his gun, was wounded in the abdomen and stomach. On healing, a fistulous opening remained in the abdominal wall, leading into the stomach, so that the contents of the latter could be inspected. Beaumont made numerous interesting and most valuable observations upon his patient. Since that time it has become customary to make fistulous openings into the stomachs of dogs when-

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[1] *The Physiology of Digestion*, 1833.

ever it is necessary to have the normal juice for examination. A silver canula is placed in the fistula, and at any time the plug closing the canula may be removed and gastric juice be obtained. In some cases the œsophagus has been occluded or excised so as to prevent the mixture of saliva with the gastric juice. Gastric juice may be obtained from human beings also in cases of vomiting or by means of the stomach-pump, but in such cases it is necessarily more or less diluted or mixed with food and cannot be used for exact analyses, although specimens of gastric juice obtained by these methods are valuable in the diagnosis and treatment of gastric troubles.

Properties and Composition of Gastric Juice.—The normal gastric secretion is a thin, colorless or nearly colorless liquid with a strong acid reaction and a characteristic odor. Its specific gravity varies, but it is never great, the average being about 1002 to 1003. Upon analysis the gastric juice is found to contain a trace of proteid, probably a peptone, some mucin, and inorganic salts, but the essential constituents are an acid (HCl) and two enzymes, pepsin and rennin. A satisfactory analysis of the human juice has not been reported, owing to the difficulty of getting proper specimens. According to Schmidt,[1] the gastric juice of dogs, free from saliva, has the following composition, given in 1000 parts:

Water	973.0
Solids	27.0
Organic substances	17.1
Free HCl	3.1
$NaCl$	2.5
$CaCl_2$	0.6
KCl	1.1
NH_4Cl	0.5
$Ca_3(PO_4)_2$	1.7
$Mg_3(PO_4)_2$	0.2
$FePO_4$	0.1

Gastric juice does not give a coagulum upon boiling, but the digestive enzymes are thereby destroyed. One of the interesting facts about this secretion is the way in which it withstands putrefaction. It may be kept for a long time, for months even, without becoming putrid and with very little change, if any, in its digestive action or in its total acidity. This fact shows that the juice possesses antiseptic properties, and it is usually supposed that the presence of the free acid accounts for this quality.

The Acid of Gastric Juice.—The nature of the free acid in gastric juice was formerly the subject of dispute, some claiming that the acidity is due to HCl, since this acid can be distilled off from the gastric juice, others contending that an organic acid, lactic acid, is present in the secretion. All recent experiments tend to prove that the acidity is due to HCl. This fact was first demonstrated satisfactorily by the analyses of Schmidt, who showed that if, in a given specimen of gastric juice, the chlorides were all precipitated by silver nitrate and the total amount of chlorine was determined, more was

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[1] Hammarsten: *Text-book of Physiological Chemistry* (translation by Mandel), 1893, p. 177.

found than could be held in combination by the bases present in the secretion. Evidently, some of the chlorine must have been present in combination with hydrogen as hydrochloric acid. Confirmatory evidence of one kind or another has since been obtained. Thus it has been shown that a number of color tests for free mineral acids react with the gastric juice: methyl-violet solutions are turned blue, congo-red solutions and test-paper are changed from red to blue, 00 tropæolin from a yellowish to a pink-red, and so on. A number of additional tests of the same general character will be found described in the laboratory handbooks of physiology.[1] It must be added, however, that lactic acid undoubtedly occurs, or may occur, in the stomach during digestion. Its presence is usually explained as being due to the fermentation of the carbohydrates, and it is therefore more constantly present in the stomach of the herbivora. The amount of free acid varies according to the duration of digestion; that is, the secretion does not possess its full acidity in the beginning, owing probably to the fact (Heidenhain) that in the first periods of digestion, while the secretion is still scanty in amount, a portion of its acid is neutralized by the swallowed saliva and the alkaline secretion of the pyloric end of the stomach (see the section on Secretion). Estimates of the maximum acidity in the human stomach are usually given as between 0.2 and 0.3 per cent. The acidity of the dog's gastric juice is greater—0.3 to 0.58 per cent.

Origin of the HCl.—The gastric juice is the only secretion of the body containing a free acid. The fact that the acid is a mineral acid makes this circumstance more remarkable, although other instances of a similar kind are known; for example, Dolium galea, a mollusc, secretes a salivary juice containing free H_2SO_4 and free HCl. When and how the HCl is formed in the stomach is still a subject of investigation. Histologically, attempts have been made to show that it is produced in the border cells of the peptic glands in the fundic end of the stomach (see Secretion). It cannot be said, however, that the evidence for this theory is at all convincing; it can be accepted only provisionally. Ingenious efforts have been made to determine the place of production of the acid by micro-chemical methods. Substances which give color reactions with acids have been injected into the blood, and sections of the mucous membrane of the stomach have then been made to determine microscopically the part of the gastric glands in which the acid is produced; but beyond proving that the acid is formed in the mucous membrane these experiments have given negative results, the color reaction for acid occurring throughout the thickness of the membrane.[2] The chemistry of the production of free HCl also remains undetermined. No free acid occurs in the blood or the lymph, and it follows, therefore, that it is manufactured in the secreting cells. It is quite evident, too, that the source of the acid is the neutral chlorides of the blood; these are in some way decomposed, the chlorine uniting with hydrogen to form HCl which is turned out upon the free surface of the stomach, while the base remains

[1] Stirling: *Outlines of Practical Physiology.*
[2] Fränkel: *Pflüger's Archiv für die gesammte Physiologie,* 1891, vol. 48, p. 63.

behind and probably passes back into the blood. The latter part of the process, the passage of the base into the blood-current, enables us to explain in part the facts, noticed by a number of observers, that the alkalinity of the blood is increased and the acidity of the urine is decreased after meals. Attempts to express the reaction which takes place in the decomposition of the chlorides are still too theoretical to merit more than a brief mention in a book of this character. According to Heidenhain, a free organic acid is secreted by the cells, which acid then acts upon and decomposes the chlorides. According to Maly, the HCl is the result of a reaction between the phosphates and the chlorides of the blood, as expressed in the two following equations:

$$NaH_2PO_4 + NaCl = Na_2HPO_4 + HCl; \text{ or,}$$
$$3CaCl_2 + 2Na_2HPO_4 = Ca_3(PO_4)_2 + 4NaCl + 2HCl.$$
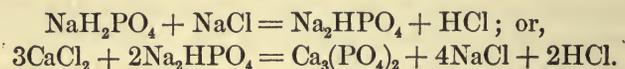
A recent theory by Liebermann supposes that the mass action of the CO_2 formed in the tissues of the gastric mucous membrane upon the chlorides, with the aid of a nucleo-albumin of acid properties which can be isolated from the gastric glands, may account for the production of the HCl. Although it is customary to speak of the HCl as existing in a free state in the gastric juice, certain differences in reaction between this secretion and aqueous solutions of the same acidity have led to the suggestion that the HCl, or a part of it at least, is held in some sort of combination with the organic (proteid) constituents of the secretion, so that its properties are modified in some minor points just as the properties of hæmoglobin are modified by the combination in which it is held in the corpuscles. The differences usually described are that in the gastric juice or in mixtures of HCl and proteid the acid does not dialyze nor distil off so readily as in simple aqueous solutions. The peptones and proteoses formed during digestion seem to combine with the acid very readily —so much so, in fact, that in certain cases specimens of gastric juice taken from the stomach, although they give an acid reaction with litmus-paper, may not give the special color reactions for free mineral acids. In such cases, however, the acid may still be able to fulfil its part in the digestion of proteids.

Nature and Properties of Pepsin.—Pepsin is a typical proteolytic enzyme which exhibits the striking peculiarity of acting only in acid media; hence peptic digestion in the stomach is the result of the combined action of pepsin and HCl. Pepsin is influenced in its action by temperature, as is the case with the other enzymes; low temperatures retard, and may even suspend, its activity, while high temperatures increase it. The optimum temperature is stated to be from 37° to 40° C., while exposure for some time to 80° C. results, when the pepsin is in a moist condition, in the total destruction of the enzyme. Pepsin has never been isolated in sufficient purity for satisfactory analysis. It may be extracted, however, from the gastric mucous membrane by a variety of methods and in different degrees of purity and strength. The commercial preparations of pepsin consist usually of some form of extract of the gastric mucous membrane to which starch or sugar of milk has been added. Laboratory preparations are usually made by mincing thoroughly the mucous membrane and then extract-

ing for a long time with glycerin. Glycerin extracts, if not too much diluted with water or blood, keep for an indefinite time. Purer preparations of pepsin have been made by what is known as "Brücke's method," in which the mucous membrane is minced and is then self-digested with a 5 per cent. solution of phosphoric acid. The phosphoric acid is precipitated by the addition of lime-water, and the pepsin is carried down in the flocculent precipitate. This precipitate, after being washed, is carried into solution by dilute hydrochloric acid, and a solution of cholesterin in alcohol and ether is added. The cholesterin is precipitated, and, as before, carries down with it the pepsin. This precipitate is collected, carefully washed, and then treated repeatedly with ether, which dissolves and removes the cholesterin, leaving the pepsin in aqueous solution. This method is interesting not only because it gives the purest form of pepsin, but also in that it illustrates one of the properties of this enzyme—namely, the readiness with which it adheres to precipitates occurring in its solutions. Pepsin illustrates very well two of the general properties of enzymes that have been described (p. 219): first, its action is incomplete, the accumulation of the products of digestion inhibiting further activity at a certain stage; and, secondly, a small amount of the pepsin, if given sufficient time and the proper conditions, will digest a very large amount of proteid.

Artificial Gastric Juice.—In studying peptic digestion it is not necessary for all purposes to establish a gastric fistula to get the normal secretion. The active agents of the normal juice are pepsin and acid of a proper strength; and, as the pepsin can be extracted and preserved in various ways, and the HCl can easily be made of the proper strength, an artificial juice can be obtained at any time which may be used in place of the normal secretion for many purposes. In laboratory experiments it is customary to employ a glycerin extract of the gastric mucous membrane, and to add a small portion of this extract to a large bulk of 0.2 per cent. HCl. The artificial juice thus made, when kept at a temperature of from 37° to 40° C., will digest proteids rapidly if the preparation of pepsin is a good one. While the strength of the acid employed is generally from 0.2 to 0.3 per cent., digestion will take place in solutions of greater or less acidity. Too great or too small an acidity, however, will retard the process; that is, there is for the action of the pepsin an optimum acidity which lies somewhere between 0.2 and 0.5 per cent. Other acids may be used in place of the HCl—for example, nitric, phosphoric, or lactic—although they are not so effective, and the optimum acidity is different for each; for phosphoric acid it is given as 2 per cent.

Action of Pepsin-Hydrochloric Acid on Proteids.—It has been known for a long time that solid proteids, such as boiled eggs, when exposed to the action of a normal or an artificial gastric juice, swell up and eventually pass into solution. The soluble proteid thus formed was known not to be coagulated by heat; it was remarkable also for being more diffusible than other forms of soluble proteids, and was further characterized by certain positive and negative reactions which will be described more explicitly farther on. This end-product of digestion was formerly described as a soluble proteid with properties fitting it for rapid absorption, and the name of *peptone* was

given to it. It was quickly found, however, that the process was complicated —that in the conversion to so-called "peptone" the proteid under digestion passed through a number of intermediate stages. The intermediate products were partially isolated and were given specific names, such as *acid-albumin*, *parapeptone*, and *propeptone*. The two latter names, unfortunately, have not always been used with the same meaning by authors, and latterly they have fallen somewhat into disuse, although they are still frequently employed to indicate some one or other of the intermediate stages in the formation of peptones. The most complete investigation of the products of peptic digestion, and of proteolytic digestion in general, we owe to Kühne and to those who have followed along the lines he laid down, among whom may be mentioned Chittenden and Neumeister. Their work has thrown new light upon the whole subject and has developed a new nomenclature. In our account of the process we shall adhere to the views and terminology of this school, as they seem to be generally adopted in most of the recent literature. It is well, however, to add, by way of caution, that investigations of this character are still going on, and the views at present accepted are liable, therefore, to changes in detail as our experimental knowledge increases. Without giving the historical development of Kühne's theory, it may be said that at present the following steps in peptic digestion have been described: The proteid acted upon, whether soluble or insoluble, is converted first to an acid-albumin (see Chemical section) to which the name *syntonin* is usually given. In artificial digestions the solid proteid usually first swells up from the action of the acid, and then slowly dissolves. Syntonin has the general properties of acid-albumins, of which properties the most characteristic is that the albumin is precipitated upon neutralizing the solution with dilute alkali. If, in the beginning of a peptic digestion, the liquid is neutralized, a more or less abundant precipitate of syntonin will form, the quantity depending upon the stage of digestion. The formation of syntonin is due mainly to the action of the HCl, although the acid seems to be much more effective in combination with pepsin than in simple aqueous solutions of the same strength. Syntonin in turn, under the influence of the pepsin, takes up water and undergoes hydrolytic cleavage, with the formation of two soluble proteids known together as *primary albumoses* or *proteoses*,[1] and separately as *proto-proteose* and *hetero-proteose*. Each of these proteids again takes up water and undergoes cleavage, with the formation of a second set of soluble proteids known as *secondary proteoses*, in contradistinction to the primary proteoses, but to which the specific name of *deutero-proteoses* is given. Finally, the deutero-proteose, or more properly the deutero-proteoses, again undergo hydrolytic cleavage, with the formation of what are known as *peptones*. Peptic digestion can go no farther than the formation of peptones, but we shall find later that other proteolytic enzymes

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[1] The term *proteose* is used by some authors in place of the older name *albumose*, as it has a more general significance. According to this usage the name *albumose* is given to the proteoses formed from albumin, *globulose* to those formed from globulin, etc., while *proteose* is a general term applying to the intermediate products from any proteid.

(trypsin, for example) are capable of splitting up a part of the peptones still further. The fact that trypsin can act upon only a part of the peptone shows that this latter substance is either a mixture of at least two separate although closely-related peptones, to which the names of *anti-peptone* and *hemi-peptone*[1] have been given, or it is a compound containing such hemi- and anti- groups, and capable, under the action of trypsin, of splitting, with the formation of hemi-peptone and anti-peptone (Neumeister). If we consider peptic digestion alone, this distinction is unnecessary. The final products of peptic digestion are therefore spoken of usually simply as peptones, although the name *ampho-peptone* is also frequently used to emphasize the fact that two distinct varieties of peptone are probably present. This description of the steps in peptic digestion may be made more intelligible by the following schema, which is modified somewhat from that given by Neumeister:[2]

Proteid.
|
Syntonin.

(Primary proteoses) = Proto-proteose.	Hetero-proteose.
(Secondary proteoses) = Deutero-proteose.	Deutero-proteose.
(Ampho-peptones) = Peptone.	Peptone.

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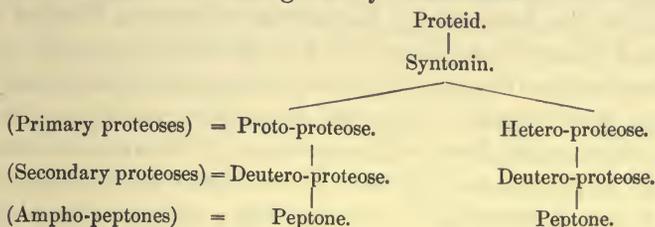
[1] Kühne's full theory of proteolytic digestion assumes that the original proteid molecule contains two atomic groups, the hemi- and the anti- group. Proteolytic enzymes split the molecule so as to give a hemi- and an anti- compound, each of which passes through a proteose stage into its own peptone. A condensed schema of the hypothetical changes would be as follows:

Proteid.
|

Anti-albumose.	Hemi-albumose.
Anti-peptone.	Hemi-peptone.

Ampho-peptone.
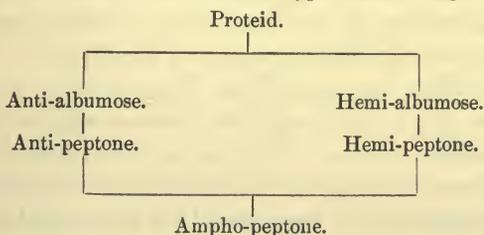
In the detailed description of proteolysis given above, primary and secondary proteoses are presumably, according to this schema, mixtures in varying proportions of hemi- and anti- compounds, or, in other words, they are ampho-proteoses. No good way of separating the anti- from the hemi- compounds has been discovered except to digest them with trypsin. By this means each compound is converted to its proper peptone, and by the continued action of the trypsin the hemi-peptone is split into much simpler bodies (p. 241), only anti-peptone being left in solution. The conception of a proteid molecule with hemi- and anti- groups and the splitting into hemi- and anti-albumose is mainly an inference backward from the fact that there are two distinct peptones, one of which, hemi-peptone, is acted upon by trypsin, while the other is not so acted upon. The details of the splitting of the proteid under the influence of pepsin are still further complicated by the fact that in some cases a part of the proteid remains undissolved, forming a highly resistant substance to which the name *antalbumid* has been given. It has been shown that if this substance is dissolved in sodium carbonate and then submitted to the action of trypsin, only anti-peptone is formed, indicating that it contains none of the hemi- group. In fact, the properties of antalbumid show that it is a peculiar modification of the anti- group which may arise during the cleavage of the proteid molecule, and may vary greatly in quantity in different digestions.

[2] *Lehrbuch der physiologischen Chemie*, 1893, p. 187.

According to this schema, peptic digestion, after the syntonin stage, consists in a succession of hydrolytic cleavages whereby soluble proteids (proteoses and peptones) are produced of smaller and smaller molecular weights. It is possible, of course, that the steps in this process may be more numerous than those represented in the schema, but the general nature of the changes seems to be established beyond question. Moreover, it is easy to understand that the products of digestion in any given case will vary with the stage at which the examination is made. Sufficiently early in the process one may find mainly syntonin, or syntonin and primary proteoses; later the deutero-proteoses and peptones may occur alone or with mere traces of the first products. The whole process is more or less progressive, although it must be understood that the first and the last products may coexist in the same liquid; that is, a part of the original proteid may be well on toward the last stages of the action while another part is in the first stages. It is worth emphasizing also that in artificial digestions with pepsin, no matter how long the action is allowed to go on, the final product is always a mixture of peptones and proteoses (deutero-proteose). Even when provision is made to dialyze off the peptone as it forms, thus simulating natural digestion, the final result, according to Chittenden and Amerman,[1] is still a mixture of proteose and peptone. The extent of peptic digestion in the body will be spoken of presently in connection with a résumé of the physiology of gastric digestion. In general, it may be said that from a physiological standpoint the object of the whole process is to get the proteids into a form in which they can be absorbed more easily. The properties and reactions of peptones and proteoses will be found stated in the Chemical section. It may serve a useful end, however, to give here some of their properties, in order to emphasize the nature of the changes caused by the pepsin.

Peptones.—The name "peptones" was formerly given to all the products of peptic digestion after it had passed the syntonin stage—that is, to the proteoses as well as the true peptones. Commercially, the word is still used in this sense, the preparations sold as peptones being generally mixtures of proteoses and peptones. True peptones, in the sense used by Kühne, are distinguished chemically by certain reactions. Like the proteoses, they are very soluble, they are not precipitated by heating, and they give a red biuret reaction (see *Reactions of Proteids,* Chemical section). They are distinguished from the primary proteoses by not giving a precipitate with acetic acid and potassium ferrocyanide, and from the whole group of proteoses by the fact that they are not thrown down from their solutions by the most thorough saturation of the liquid with ammonium sulphate. This last reaction gives the only means for the complete separation of the peptones from the proteoses. The peptones, indeed, may be defined as being the products of proteolytic digestion which are not precipitated by saturation of the liquid with ammonium sulphate. The validity of this reaction has lately been called in question. It has been pointed out that, although the primary proteoses are readily precipitated by this salt, the deutero-proteoses, under certain circumstances at least, are not precipitated, and cannot

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[1] *Journal of Physiology,* vol. xiv., 1893, p. 483.

therefore be distinguished or separated from the so-called " true peptones." We must await further investigations before attempting to come to any conclusion upon this point. It is well to bear in mind that the change from ordinary proteid to peptone evidently takes place through a number of intermediate steps, and the word *peptone* is meant to designate the final product. Whether this final product is a chemical individual with properties separating it from all the intermediate stages is perhaps not yet fully known, but, provisionally at least, we may adopt Kühne's definition, outlined above, of what constitutes peptone, as it seems to be generally accepted in current literature. Peptones are characterized by their diffusibility, and this property is also possessed, although to a less marked extent, by the proteoses. Recent work by Chittenden,[1] in which he corroborates results published simultaneously by Kühne, shows the following relative diffusibility of peptones and proteoses. The solutions used were approximately 1 per cent.; they were dialyzed in parchment tubes against running water for from six to eight hours, and the loss of substance was determined and expressed in percentages of the original amount. Proto-proteose gave a loss of 5.09 per cent.; deutero-proteose, 2.21 per cent.; peptone, 11 per cent.

Several elementary analyses of proteoses and peptones have been reported, but they cannot be accepted as final, owing to the fact that the substances analyzed were probably mixtures, and not chemical individuals. The following analyses, reported by Chittenden,[2] will serve to show the relative percentage composition of these bodies:

Phyto-vitellin, a Crystallized Proteid extracted from Hemp-seed.

	Mother-proteid.	Proto-vitellose.	Deutero-vitellose.	Peptone.
C	51.63	51.55	49.78	49.40
H	6.90	6.73	6.73	6.77
N	18.78	18.90	17.97	18.40
S	0.90	1.09	1.08	0.49
O	21.79	21.73	24.44	24.94

The most striking differences in composition observed in passing from the mother-proteid to the peptones are the progressive decrease in the percentage of carbon and the increase in the percentage of oxygen. Both these facts are in accord with the general theory that proteolysis consists essentially in a series of hydrolytic cleavages.

Rennin.—In addition to pepsin the gastric secretion contains an enzyme which is characterized by its coagulating action upon milk. It has long been known that milk is curdled by coming into contact with the mucous membrane of the stomach. Dried mucous membrane of the calf's stomach, when stirred in with fresh milk, will curdle the latter with astonishing rapidity, and this property has been utilized in the manufacture of cheese. Hammarsten discovered that this action is due to the presence of a specific enzyme which exists ready formed in the membrane of the sucking-calf's stomach, and which is present

[1] *Journal of Physiology*, vol. xiv., 1893, p. 502.
[2] Cartwright Lectures, *New York Medical Record*, April, 1894.

in a preparatory form (rennin-zymogen) in stomachs of all mammals. This enzyme has been given several names; *rennin* seems preferable to any other, and is the term most commonly employed. Rennin may be obtained from the stomach by self-digestion of the mucous membrane or by extracting it with glycerin. Such extracts usually contain both pepsin and rennin, but the two have been separated successfully, most easily by the prolonged action of a temperature of 40° C. in acid solutions, which destroys the rennin, but not the pepsin. Good extracts of rennin cause clotting of milk with great rapidity at a temperature of 40° C., the milk (cow's milk), if undisturbed, setting first into a solid clot, which afterward shrinks and presses out a clear yellowish liquid, the whey; with human milk, however, the curd is much less firm, being deposited in the form of loose flocculi. The whole process resembles the clotting of blood not only in the superficial phenomena, but also in the character of the chemical changes. Briefly, what happens is that the rennin acts upon a soluble proteid in the milk known usually as *casein*, but by some called "caseinogen," and changes this proteid to an insoluble modification which is precipitated as the curd. The chemistry of the change is not completely understood, and there is an unfortunate want of agreement in the terminology used to designate the products of the action. It has been shown that, as in the case of blood, curdling cannot take place unless lime salts are present. What seems to occur is as follows: Casein is a complex substance belonging to the group of nucleo-albumins, and when acted upon by rennin it undergoes hydrolytic cleavage, with the formation of two proteid bodies, paracasein and whey proteid. The first of these bodies forms with calcium salts an insoluble compound which is precipitated as the curd; the second remains behind in solution in the whey. It will be seen that this theory supposes the action to be parallel with that occurring in blood-coagulation, where fibrin ferment causes a cleavage of the fibrinogen molecule, a part uniting with calcium to form the insoluble fibrin, and a part—much the smaller part—remaining in solution in the serum as fibrin-globulin. It should be added that casein is also precipitated from milk by the addition of an excess of acid. The curdling of sour milk in the formation of bonnyclabber is a well-known illustration of this fact. When milk stands for some time the action of bacteria upon the milk-sugar leads to the formation of lactic acid, and when this acid reaches a certain concentration it causes the precipitation of the casein. One might suppose that the curdling of milk in the stomach is caused by the acid present in the gastric secretion, but it has been shown that perfectly neutral extracts of the gastric mucous membrane will curdle milk quite readily.

So far as our positive knowledge goes, the action of rennin is confined to milk. Casein constitutes the chief proteid constituent of milk, and has therefore an important nutritive value. It is interesting to find that before its peptic digestion begins the casein is acted upon by an altogether different enzyme. The value of the curdling action is not at once apparent, but we may suppose that casein is more easily digested by the proteolytic enzymes after it has been brought into a solid form. The action of rennin goes no

further than the curdling ; the digestion of the curd is carried on by the pepsin, and later, in the intestines, by the trypsin, with the formation of proteoses and peptones as in the case of other proteids.

Action of Gastric Juice on Carbohydrates and Fats.—The gastric juice itself has no direct action upon carbohydrates ; that is, it does not contain an amylolytic enzyme. It is possible, nevertheless, that some digestion of carbohydrates goes on in the stomach, for, as has been seen, the masticated food is thoroughly mixed with saliva before it is swallowed. The portion that enters the stomach in the beginning of digestion, when the acidity of the contents is small (see p. 227), may continue to be acted upon by the ptyalin. This effect, however, cannot be considered important, since the acidity of the contents of the stomach must soon reach a point sufficient to suspend, and then to destroy, the ptyalin. It should be added, however, that Lusk [1] has shown that cane-sugar can be inverted to dextrose and levulose in the stomach. The importance of this process of inversion, and the means by which it is accomplished, will be described more in detail when speaking of the digestion of sugars in the small intestine (p. 247). Upon the fats also gastric juice has no direct digestive action. According to the best evidence at hand, neutral fats are not split in the stomach, nor are they emulsified or absorbed. Without doubt, the heat of the stomach is sufficient to liquefy most of the fats eaten, and the movements of the stomach, together with the digestive action of its juice on the proteids and albuminoids with which the fats are often mixed, bring about such a mechanical mixture of the fats and oils with the other elements of the chyme as facilitates the more rapid digestion of these substances in the intestine.

Action of Gastric Juice on the Albuminoids.—Gelatin is, from a nutritive standpoint, the most important of the albuminoids. Its nutritive value is stated briefly on page 215. It has been shown that this substance is acted upon by pepsin in a way practically identical with that described for the proteids. Intermediate products are formed similar to the albumoses, which products have been named *gelatoses* [2] or *glutoses ;* [3] these in turn may be converted to gelatin peptones. It is stated that the action of pepsin is confined almost, if not entirely, to changing gelatin to the gelatose stage. The proteolytic enzyme of the pancreatic secretion, however carries the change to the peptone stage much more readily.

Why does the Stomach not Digest Itself ?—The gastric secretion will readily digest a stomach taken from some other animal, or under certain conditions it may digest the stomach in which it is secreted. If, for instance, an animal is killed while in full digestion, the stomach may undergo self-digestion, especially if the body is kept warm. This phenomenon has been observed in human cadavers. It has been shown also that if a portion of the stomach is deprived of its circulation by an embolism or a ligature, it may be attacked by the secretion and a perforation of the stomach-wall may result. How,

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[1] Voit: *Zeitschrift für Biologie*, vol. xxviii., 1891, p. 269.

[2] Chittenden and Solley: *Journal of Physiology*, vol. xii., 1891, p. 23.

[3] Klug: *Pflüger's Archiv für die gesammte Physiologie*, vol. 48, 1891, p. 100.

then, under normal conditions, is the stomach protected from corrosion by its own secretion? The question has given rise to much discussion, and in reality it deals with one of the fundamental properties of living matter, for the same question must be extended to take in the non-digestion of the small intestine by the alkaline pancreatic secretion, the non-digestion of the digestive tracts of the invertebrates, and the case of the unicellular animals in which there is formed within the animal's protoplasm a digestive secretion which digests foreign material, but does not affect the living substance of the cell. In the particular case under consideration—namely, the protection of the mammalian stomach from its own secretion—explanations of the following character have been offered: It was suggested (Hunter) that the " principle of life " in living things protected them from digestion. This suggestion cannot be considered seriously at the present day, since it implies that living matter is the seat of a special force, the so-called " vital principle," different from the forms of energy acting upon matter in general. Appeals of this kind to an unknown force in explanation of the properties of living matter are not now permissible in the science of physiology. Moreover, it was shown by Bernard that the hind leg of a living frog introduced into a dog's stomach through a fistula undergoes digestion. The same thing will happen, it may be added, if the leg is put into a vessel containing an artificial gastric juice at the proper temperature. Bernard's theory was that the epithelium of the stomach acts as a protection to the organ, preventing the absorption of the juice. Others believe that the mucus formed by the gastric membrane acts as a protective covering; while still another theory holds that the alkaline blood circulating through the organ saves it from digestion, since it neutralizes the acid of the secretion as fast as it is absorbed, and it is known that pepsin can digest only in an acid medium. None of these explanations is sufficient. The last explanation is unsatisfactory because it does not explain the immunity of the small intestine from digestion by the alkaline pancreatic juice, or the protection of the infusoria from their own digestive secretion. The mucous theory is inadequate, as we cannot believe that by this means the protection could be as complete as it is; and, moreover, this theory does not admit of a general application to other cases. The epithelium theory simply changes the problem a little, as it involves an explanation of the immunity of the living epithelial cells. It is well known that in the dead stomach the epithelial lining is no longer a protection against digestion, so that we are led to believe that there is nothing peculiar in the composition of epithelial cells, as compared with other tissues, to account for their exemption under normal conditions. When we come to consider all the evidence, nothing seems clearer than that the protection of the living tissue is in every case due to the properties of its living structure. So long as the tissue is alive, it is protected from the action of the digesting secretion, but the ultimate physical or chemical reason for this property is yet to be discovered. In the case of the mammalian stomach it is quite probable that the lining epithelial cells are especially modified to resist the action of the digestive secretion, but, as has

just been said, they lose this property as soon as they undergo the change from living to dead structure. The digestion of the living frog's leg in gastric juice, and similar instances, do not affect this general idea, since, as Bernard himself pointed out, what happens in this case is that the tissue is first killed by the acid and then undergoes digestion. On the other hand, Neumeister has shown that a living frog's leg is not digested by strong pancreatic extracts of weak alkaline reaction, since under these conditions the tissues are not injured by the slightly alkaline liquid. When it is said that the exemption of living tissues from self-digestion is due to the peculiarities of their structure, it must not be supposed that this is equivalent to referring the whole matter to the action of a mysterious vital force. On the contrary, all that is meant is that the structure of living protoplasmic material is such that the action of the digestive secretion is prevented, possibly because it is not absorbed, this result being the outcome of the physical and chemical forces exhibited by matter with this peculiar structure. While a statement of this kind is not an explanation of the facts in question, and indeed amounts to a confession that an explanation is not at present possible, it at least refers the phenomenon to the action of known properties of matter.

General Remarks upon the Physiology of the Stomach.—From the foregoing account it will be seen that, speaking generally, the functions of the stomach are in part to act chemically upon the proteids, and in part, by the combined action of its secretion and its muscular movements, to get the food into a physical condition suitable for subsequent digestion in the intestine. The material sent out from the stomach (chyme) must be quite variable in composition, but physically the action of the stomach has been such as to reduce it to a liquid or semi-liquid consistency. The extent of the true digestive action of gastric juice on proteids is not now believed to be so complete as it was formerly thought to be. Examination of the chyme shows that it may contain quantities of undigested or only partially digested proteid, complete digestion being effected in the intestines. Moreover, artificial peptic digestion of proteids under the most favorable conditions shows that only a portion is ever converted to peptone, most of it remaining in the proteose stage. It has been suggested, therefore, that gastric digestion of proteids is largely preparatory to the more complete action of the pancreatic juice, whose enzyme (trypsin) has more powerful proteolytic properties. In accordance with this idea, it has been shown that an animal can live and thrive without a stomach. Several cases [1] are on record in which the stomach was practically removed by surgical operations, the œsophagus being stitched to the duodenum. The animals did well and seemed perfectly normal. Experiments of this character do not, of course, show that the stomach is useless in digestion; they demonstrate only that in the animals used it is not absolutely essential. The reason for this will better be appreciated after the digestive properties of pancreatic secretion have been studied.

[1] Ludwig and Ogata: *Archiv für Anatomie und Physiologie*, 1883, p. 89; and Carvallo and Pachon: *Archives de Physiologie normale et pathologique*, 1894, p. 106.

D. Intestinal Digestion.

After the food has passed through the pyloric orifice of the stomach and has entered the small intestine it undergoes its most profound digestive changes. Intestinal digestion is carried out mainly while the food is passing through the small intestine, although, as we shall see, the process is completed during the slower passage through the large intestine. Intestinal digestion is effected through the combined action of three secretions—namely, the pancreatic juice, the bile, and the intestinal juice. The three secretions act together upon the food, but for the sake of clearness it is advisable to consider each one separately as to its properties and its digestive action.

Composition of Pancreatic Juice.—Pancreatic juice is the secretion of the pancreatic gland. In man the main duct of the gland opens into the duodenum, in common with the bile-duct, about 8 to 10 cm. below the opening of the pylorus. In some of the other mammals the arrangement is different: in dogs, for example, there are two ducts, one opening into the duodenum, together with the bile-duct, about 3 to 5 cm. below the opening of the pylorus, and one some 3 to 5 cm. farther down. In rabbits the principal duct opens separately into the duodenum about 35 cm. below the opening of the bile-duct. For details as to the act of secretion, its time-relations to the ingestion of food, its quantity, etc., the reader is referred to the section on Secretion. Most of our exact knowledge of the properties of the pancreatic secretion has been obtained either from experiments upon lower animals, especially the dog and the rabbit, in which it is possible to establish a pancreatic fistula and to collect the normal juice, or from experiments with artificial pancreatic juice prepared from extracts of the gland. Various methods have been used in making pancreatic fistulæ: usually the main duct of the gland, which in the two animals named is separate from the bile-duct, is exposed and a canula is inserted. A better method, devised by Heidenhain, consists in cutting out the piece of duodenum into which the main duct opens and sewing this isolated piece to the abdominal wall so as to make a permanent fistula, the continuity of the intestinal tract in this case being re-established, of course, by sutures. A simple method of obtaining normal pancreatic juice from the rabbit is described by Ratchford.[1] In his method the portion of the duodenum into which the main duct opens is resected and cut open along the border opposite to the mesenteric attachment. The mouth of the duct is seen as a small papilla projecting from the surface of the mucous membrane. Through the papilla a small glass canula may be passed into the duct, and the secretion, which flows slowly, may be collected for several hours. The total quantity obtainable by this means from a rabbit is small—about 1 c.c.—but it is sufficient for the demonstration of some of the important properties of pancreatic juice, especially its action upon fats. As obtained by these methods, the secretion is found to be a clear, colorless, alkaline liquid. The secretion obtained from dogs is thick and glairy, and forms a coagulum upon standing,

[1] *Journal of Physiology*, vol. xii., 1891, p. 72.

while that from rabbits is a thin, perfectly colorless liquid which does not form a clot. In dogs the secretion from a permanent fistula soon becomes thinner than it was when the fistula was first established, and this change in its consistency is accompanied by a corresponding variation in specific gravity. The specific gravity (dog) of the juice from a temporary fistula is given at 1030; from a permanent fistula, at 1010 to 1011. The secretion coagulates upon being heated, owing to the proteids held in solution, and it undergoes putrefaction very quickly, so that it cannot be kept for any length of time. The analysis of the secretion most frequently quoted is that given by C. Schmidt, as follows:

Pancreatic Juice (Dog).

Constituents.	Immediately after establishing fistula.	From permanent fistula.
Water	900.76	980.45
Solids	99.24	19.55
Organic substances	90.44	12.71
Ash	8.80	6.84
Sodium carbonate	0.58	3.31
Sodium chloride	7.35	2.50
Calcium, magnesium, and sodium phosphates	0.53	0.08

The composition of normal human pancreatic juice has not been determined completely, owing to the rarity of opportunities of obtaining the secretion. Several partial analyses have been reported. According to Zawadsky,[1] the composition of the secretion in a young woman was as follows:

In 1000 parts.

Water	864.05
Organic substances	132.51
Proteids	92.05
Salts	3.44

The organic substances held in the secretion are in part of an albuminous nature, since they coagulate upon heating, but the exact nature of the proteid or proteids has not been determined satisfactorily. The most important of the organic substances—the essential constituents, indeed, of the whole secretion— are three enzymes acting respectively upon the proteids, the carbohydrates, and the fats. The proteolytic enzyme is called "trypsin;" the amylolytic enzyme is described under different names: "amylopsin" is perhaps the best, and will be adopted in this section; for the fat-splitting enzyme we shall use the term "steapsin." Owing to the presence of these enzymes the pancreatic secretion is capable of exerting a digestive action upon each of the three important classes of food-stuffs.

Trypsin.—Trypsin is a more powerful proteolytic enzyme than pepsin. Unlike the latter, trypsin acts best in alkaline media, but it is effective also in neutral liquids, or even in solutions not too strongly acid. Trypsin is affected by changes in temperature like the other enzymes, its action being retarded by cooling and being hastened by warming. There is, however, a temperature,

[1] *Centralblatt für Physiologie,* vol. 5, 1891, p. 179.

which may be called the optimum temperature, at which the trypsin acts most powerfully; if, however, the temperature is raised to as much as 70° to 80° C., the enzyme is destroyed entirely. Trypsin has never been isolated in a condition sufficiently pure for analysis, so that its chemical composition is unknown. Extracts containing trypsin can be made from the gland very easily and by a variety of methods. The usual laboratory method is to mince the gland and to cover it with glycerin for some time. In using this and other methods for preparing trypsin extracts it is best not to take the perfectly fresh gland, but to keep it for a number of hours before using. The reason for this is that the enzyme exists in the fresh gland in a preparatory stage, a zymogen (see section on Secretion), which in this case is called "trypsinogen." Upon standing, the latter is slowly converted to trypsin—a process which may be hastened by the action of dilute acids and by other means. An artificial pancreatic juice is prepared usually by adding a small quantity of the pancreatic extract to an alkaline liquid; the liquid usually employed is a solution of sodium carbonate of from 0.2 to 0.5 per cent. To prevent putrefactive changes, which come on with such readiness in pancreatic digestions, a few drops of an alcoholic solution of thymol may be added. A mixture of this kind, if kept at the proper temperature, digests proteids very rapidly, and most of our knowledge of the action of trypsin has been obtained from a study of the products of such digestions.

Products of Tryptic Digestion.—Tryptic digestion resembles peptic digestion in that proteoses and peptones are the chief products formed, but the two processes differ in a number of details. The naked-eye appearances, in the first place, are different in cases in which the proteid acted upon is in a solid form; for while in the pepsin-hydrochloric digestion the proteid swells up and gradually dissolves, under the action of trypsin it does not swell, but suffers erosion, as it were, the solid mass of proteid being eaten out until finally only the indigestible part remains, retaining the shape of the original mass, but falling into fragments when shaken. In the second place, the hydrolytic cleavages seem to be of a more intense nature. In peptic digestion, after the syntonin stage is passed, there is a gradual change to peptone through the intermediate primary and secondary proteoses. Under the influence of trypsin, according to the most recent experiments, the solid proteid undergoes a transformation directly to secondary proteoses (deutero-proteoses), the intermediate stages being skipped. It was formerly thought that the solid proteid was converted first into a soluble proteid, and that if the solution was alkaline some alkali-albumin was formed, precipitable by neutralization, and comparable to the syntonin of pepsin-hydrochloric digestion. This soluble proteid was thought to be split into proteoses of the hemi- and anti- groups which were then converted to the corresponding peptones, according to Kühne's schema (p. 231). There seems to be no doubt that with the proteid most frequently used in artificial digestion—namely, fibrin from coagulated blood—the first effect is a conversion to a soluble globulin-like form of proteid; but Neumeister finds that this does not happen with other proteids, and he thinks that in the case of fibrin it is not due to a

true digestive action of trypsin, but to a partial solution of the fibrin by the inorganic salts in the liquid. In general, however, the preliminary stage of a soluble proteid is missed, as also is that of the primary proteoses. The proteid falls at once by hydrolytic cleavage into deutero-proteoses, and these in turn are transformed to peptones (ampho-peptones). Just at this point comes in one of the most characteristic differences between the action of pepsin and that of trypsin. Pepsin cannot affect further the ampho-peptones, but trypsin may act upon the supposed hemi- constituent and split it up, with the formation of a number of much simpler non-proteid bodies, most of which are amido-acids. The final products of prolonged tryptic digestion are, first, a peptone which cannot further be decomposed by the enzyme and which constitutes what is known as *anti-peptone*, and, second, a number of simpler organic substances, mainly amido-acids, that come from the splitting of that part of the peptone which can be acted upon by the trypsin, and which constitutes what is known as *hemi-peptone*. It may be remarked in passing that hemi-peptone has not been isolated. Ampho-peptones containing both anti- and hemi-peptones are formed in peptic digestion, and they may be obtained from tryptic digestion if it is not allowed to go too far; anti-peptone, on the other hand, may be obtained from tryptic digestion which has been permitted to go on until the hemi-peptone has been completely destroyed, but no good method is known by which hemi-peptone can be isolated from solutions containing both it and the anti- form. The simpler products formed by the breaking up of the hemi-peptone molecule under the influence of the trypsin can be formed, in part at least, in the laboratory by processes which are known to cause hydrolytic decompositions. It is probable, therefore, that these substances may be looked upon as products of the hydrolytic cleavage of hemi-peptone. They are of smaller molecular weight and of simpler structure than the peptone molecule from which they are formed. A tabular list of these bodies, taken from Gamgee,[1] is given. The list includes only those substances which have actually been isolated; it is possible that others exist:

Final Products (other than Peptones) of the Action of Trypsin on Albuminous and Albuminoid Bodies.

Bodies derived from the fatty acids.	Bases.	Organic body of unknown composition.	Aromatic bodies.
Amido-caproic acid (leucin). Amido - valerianic acid (butalanin). Amido-succinic acid (aspartic acid). Amido-pyrotartaric acid (glutamic acid). (Diamido-acetic acid ?)	Lysin. Lysatinin. NH₃.	Tryptophan (gives a red color on the addition of chlorine-water, and violet with bromine-water).	Paroxyphenylamidopropionic acid (tyrosin).

Of these substances, the ones longest known and most easily isolated are leucin ($C_6H_{13}NO_2$) and tyrosin ($C_9H_{11}NO_3$). The chemical composition and proper-

[1] *A Text-book of the Physiological Chemistry of the Animal Body*, 1893, vol. ii. p. 230.

ties of these and the other products are described in the Chemical section. Leucin and tyrosin have been found in the contents of the intestines, and it is probable, therefore, that the splitting of the hemi-peptone which takes place so readily in artificial tryptic digestions occurs also, to some extent at least, within the body, although we have no accurate estimates of the amount of peptone destroyed in this way under normal conditions. On the supposition that the production of leucin, tyrosin, and the other amido- bodies is a normal result of tryptic digestion within the body, it is interesting to inquire what physiological value, if any, is to be attributed to these substances. At first sight the formation of these amido- bodies from the valuable peptone would seem to be a waste. Peptone we know may be absorbed into the blood, and may then be used to form or repair proteid tissue, or to furnish energy to the body upon oxidation, but leucin and tyrosin and the other products of the breaking up of the hemi-peptone are far less valuable as sources of energy, and so far as we know they cannot be used to form or repair proteid tissue. But we must be careful not to jump too hastily to the conclusion that the splitting of the hemi-peptone is useless. It remains possible that a wider knowledge of the subject may show that the process is of distinct value to the body, although it must be confessed that no plausible suggestion as to its importance has yet been made. In addition to any possible functional value which these amido-bodies may possess, their occurrence in proteolysis is of immense interest to the physiologist. Some of them are of a constitution simple enough to be studied by exact chemical methods, and the hope is entertained that through them a clearer knowledge may be obtained of the structure of the proteid molecule. It should be added that not only are these amido- bodies found in the alimentary canal as products of tryptic digestion, but that they, or some of them, occur also in other parts of the body, especially under pathological conditions, and that, furthermore, they occur among the products of the destruction of the proteid molecule by laboratory methods or by the action of bacterial organisms. The theoretical importance of the base lysatinin will be referred to again later, when speaking of the origin of urea in the body. The processes of tryptic digestion outlined above are represented in brief in the following schema, taken from Neumeister : [1]

<div style="text-align:center">

Proteid.
|
Deutero-albumoses.
|
Ampho-peptone.
|

Anti-peptone.   Hemi-peptone.
                            |

Leucin.   Tyrosin.   Aspartic acid.   Tryptophan, etc.

</div>
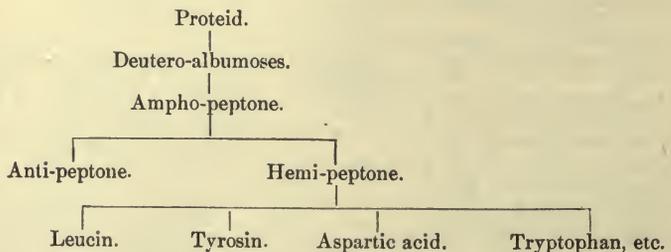
It may be said in conclusion that trypsin produces peptone from proteids more readily than does pepsin. Under normal conditions it is probable that most

[1] *Lehrbuch der physiologischen Chemie,* 1893, p. 200.

of the proteid of the food receives its final preparation for absorption in the small intestine, under the influence of this enzyme.[1]

Albuminoids.—Gelatin and the other albuminoids are acted upon by trypsin, the products being similar in general to those formed from the proteids. As stated on page 235, pepsin carries the digestion of gelatin mainly to the gelatose stage; trypsin, however, produces gelatin peptones. It seems probable, therefore, that the final digestion of the albuminoids also is effected in the small intestine.

Amylopsin.—The enzyme of the pancreatic secretion which acts upon starches is found in extracts of the gland, made according to the general methods already given, and its presence may be demonstrated, of course, in the secretion obtained by establishing a pancreatic fistula. The proof of the existence of this enzyme is found in the fact that if some of the pancreatic secretion or some of the extract of the gland is mixed with starch paste, the starch quickly disappears and maltose or maltose and dextrin are found in its place. Amylopsin shows the general reactions of enzymes with relation to temperature, incompleteness of action, etc. Its specific reaction is its effect upon starches. Investigation has shown that the changes caused by it in the starches are apparently the same as those produced by ptyalin. In fact, the two enzymes ptyalin and amylopsin are identical in properties as far as our knowledge goes, so that it is not uncommon, in German literature especially, to have them both described under the name of *ptyalin*. The term *amylopsin* is convenient, however, in any case, to designate the special origin of the pancreatic enzyme. As to the details of its action, it is unnecessary to repeat what has been said on page 223. The end-products of its action, as far as can be determined from artificial digestions, are a sugar, maltose ($C_{12}H_{22}O_{11},H_2O$), and more or less of the intermediate achroödextrins,

[1] The details of the cleavage of the proteid molecule under the influence of pepsin and trypsin are obviously not yet completely worked out. The general idea of Kühne is given briefly in a foot-note on page 231. An important modification of the original conception is represented in a theoretical schema given by Neumeister, which is here reproduced. According to this diagram, each proteose, as well as the peptone produced in an ordinary digestion, contains both hemi- and anti- groups, and is therefore an ampho- compound. The relative amount of hemi- or anti- substance present at each stage is indicated by thick or thin lines as the case may be. While proto-proteose and the deutero-proteose and peptone arising from it are mainly composed of the hemi-group, hetero-proteose and its subsequent stages consist chiefly of the anti- grouping. The resistant compound, known as anti-albumid, which is split off from the proteid molecule in greater or less quantity, seems to have only the anti- grouping; so far as it can be converted to peptone, it yields only anti-peptone.
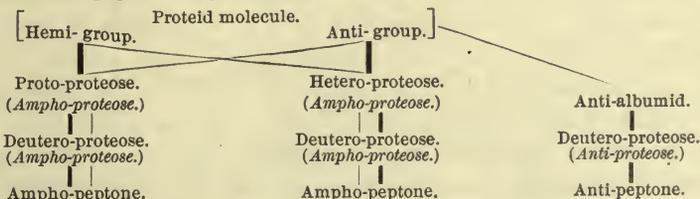
the relative amounts depending upon the completeness of digestion. As has previously been said, there are indications that under the favorable conditions of natural digestion all the starch may be changed to maltose, but possibly it is not necessary that the action should be so complete in order that the carbohydrate may be absorbed into the blood, as will be shown when we come to speak of the further action of the intestinal secretion upon maltose and the dextrins. The amylolytic action of the pancreatic juice is extremely import-ant. The starches constitute a large part of our ordinary diet. The action of the saliva upon them is probably, for reasons already given, of subordinate importance. Their digestion takes place, therefore, entirely or almost entirely in the small intestine, and mainly by virtue of the action of the amylopsin contained in the pancreatic secretion. The action of the amylopsin is supple-mented to some extent, apparently, by a similar enzyme formed in small quantities in the intestinal wall itself, the nature of which will be described presently in connection with intestinal secretion.

Steapsin.—Steapsin is the name given to a fat-splitting enzyme occurring in the pancreatic juice. It is of the greatest importance in the digestion and absorption of fats. The peculiar power of the pancreatic juice to split neutral fats with the liberation of free fatty acid was first described by Bernard. His discovery has since been corroborated for different animals, including man, by the use of normal pancreatic juice obtained from a fistula, or by the aid of the tissue of the fresh gland, or, finally, by means of extracts of the gland. When neutral fats (see Chemical section for the composition of fats) are treated with an extract containing steapsin, they take up water and then undergo cleavage (hydrolysis), with the production of glycerin and the free fatty acid found in the particular fat used. This reaction is explained by the following equation, in which a general formula for fats is used:

$$C_3H_5(C_nH_{2n+1}COO)_3 + 3H_2O = C_3H_5(OH)_3 + 3(C_nH_{2n+1}COOH).$$
$$\text{Fat.} \qquad\qquad\qquad\qquad\qquad \text{Glycerin.} \qquad\quad \text{Free fatty acid.}$$
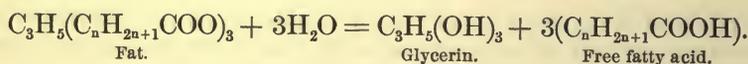
The reaction in the case of palmitin would be—

$$C_3H_5(C_{15}H_{31}COO)_3 + 3H_2O = C_3H_5(OH)_3 + 3(C_{15}H_{31}COOH).$$
$$\text{Palmitin.} \qquad\qquad\qquad\qquad \text{Glycerin.} \qquad\quad \text{Palmitic acid.}$$
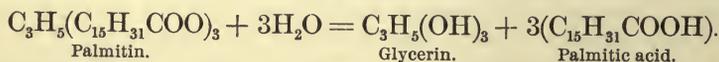
While this action is undoubtedly caused by an enzyme, it has not been possible to isolate the so-called "steapsin" in a condition of even approximate purity. As a matter of fact also, ordinary extracts of pancreas, such as the laboratory extracts in glycerin, do not usually show the presence of this enzyme unless special precautions are taken in their preparation. It would seem that steapsin is easily destroyed. With fresh normal juice or with pieces of fresh pancreas the fat-splitting effect can be demonstrated easily. One striking method of making the demonstration is to use butter as the fat to be decomposed. If butter is mixed with normal pancreatic juice or with pieces of fresh pancreas, and the mixture is kept at the body-temperature, the several fats contained in butter will be decomposed and the corresponding fatty acids will be liberated,

among them butyric acid, which is readily recognized by its familiar odor, that of rancid butter. The action of steapsin, as in the case of the other enzymes, is very much influenced by the temperature. At the body-temperature the action is very rapid. The nature of the fat also influences the rapidity of the reaction; it may be said, in general, that fats with a high melting-point are less readily decomposed than those with a low melting-point. It has been shown, however, that even spermaceti, which is a body related to the fats and whose melting-point is 53° C., is decomposed, although slowly and imperfectly, by steapsin. The fat-splitting action of the steapsin undoubtedly takes place normally in the intestines, but it must not be supposed that all the fat eaten undergoes this process. On the contrary, it is believed that a small portion only of the fats and oils is affected by the steapsin, by far the larger portion remaining unaffected and being absorbed into the blood as neutral fat. What, then, is the physiological value of steapsin in the digestion and absorption of fats? This question is difficult to answer satisfactorily if one goes into the details. In general, however, it is commonly taught that the small part of the fat split by the steapsin into fatty acid and glycerin helps to emulsify the balance of the fat and thereby renders its absorption possible. The fat-splitting action of steapsin, then, is of indirect value in digestion, and its importance can be brought out best by describing the emulsification of fats and the conditions bringing this emulsification about.

Emulsification of Fats.—An oil is emulsified when it is broken up into minute globules which do not coalesce, but which remain separate and more or less uniformly distributed throughout the medium in which they exist. Artificial emulsions can be made by shaking oil vigorously in viscous solutions of soap, mucilage, etc. Milk is a natural emulsion which separates partially on standing, some of the oil rising to the top to form cream. Bernard made the important discovery that when oil and pancreatic juice are shaken together an emulsion of the oil takes place very rapidly, especially if the temperature is about that of the body. The main cause of the emulsification has been shown to be the formation of free fatty acids due to the action of steapsin, and the union of these acids with the alkaline salts present to form soaps. This fact has been demonstrated by experiments of the following character: If a perfectly neutral oil is shaken with an alkaline solution ($\frac{1}{4}$ per cent. sodium-carbonate solution), no emulsion occurs and the two liquids soon separate. If to the same neutral oil one adds a little free fatty acid, or if one uses rancid oil to begin with and shakes it with $\frac{1}{4}$ per cent. sodium-carbonate solution, an emulsion forms rapidly and remains for a long time. Oil containing fatty acids when shaken with distilled water alone will not give an emulsion. It has been shown, moreover, by Gad and Ratchford that with a certain percentage of free fatty acids ($5\frac{1}{2}$ per cent.) rancid oil and a sodium-carbonate solution will form a fine emulsion spontaneously—that is, without shaking. Shaking, however, facilitates the emulsification when the amount of free acid varies from this optimum percentage. In what way the formation of soaps in an oily liquid causes the oil to become emulsified is still a matter

of speculation. It has been suggested that the soap forms a thin coating or membrane round the small oil-drops, thus preventing them from uniting. The splitting of the oil into small drops seems to be caused, in cases of spontaneous emulsification, by the act of formation of the soap—that is, the union of the alkali with the fatty acid—in other cases by the mechanical shaking, or by these two causes combined. The application of these facts to the action of the pancreatic juice normally in the small intestine is easily made. When the chyme, containing more or less of liquid fat, comes into contact with the pancreatic juice, a part of the oil is quickly split by the steapsin, with the formation of free fatty acids. These acids unite with the alkalies and the alkaline salts present in the secretions of the small intestine (pancreatic juice, bile, intestinal juice) to form soaps. The formation of the soaps, aided, perhaps, by the peristaltic movements of the intestine, emulsifies the remainder of the fats and thus renders them ready for absorption. It has been suggested that the proteids in solution in the pancreatic juice aid in the emulsification, but there is no experimental evidence to show that this is the case. A factor of much more importance is the influence of the bile. In man the pancreatic juice and the bile are poured into the duodenum together, and in all mammals the two secretions are mixed with the food at some part of the duodenum. Now, it has been shown beyond question that a mixture of bile and pancreatic juice will cause a splitting of fats into fatty acids and glycerin much more rapidly than will the pancreatic juice alone.[1] This effect of the bile is not due to the presence in it of a fat-splitting enzyme of its own: the bile seems merely to favor in some way the action of the steapsin contained in the pancreatic secretion. Bile aids the emulsification possibly in another way. To be efficient as emulsifiers the fatty acids must form soaps. The alkaline salts of the pancreatic juice do not appear to be in a form in which they can be used readily for this purpose. It is supposed that the alkaline salts of the bile (and the intestinal juice) are therefore made use of. The mechanism of the absorption of the emulsified fat and the importance of bile in this process will be described subsequently.

Intestinal Secretion.—The small intestine is lined with tubular glands, the crypts of Lieberkuhn, which are supposed to form a secretion of considerable importance in digestion. To obtain the intestinal secretion, or *succus entericus,* as it is often called, recourse has been had to an ingenious operation for establishing a permanent intestinal fistula. This operation, which usually goes under the name of the "Thiry-Vella fistula," consists in cutting out a small portion of the intestine without injuring its supply of blood-vessels or nerves, and then sewing the two open ends of this piece into the abdominal wall so as to form a double fistula. The continuity of the intestines is established by suture, while the isolated loop with its two openings to the exterior can be used for collecting the intestinal secretion uncontaminated by partially-digested food. The secretion is always small in quantity, and it must be

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[1] Nencki: *Archiv für experimentelle Pathologie u. Pharmakologie,* vol. 20, 1886, p. 367 ; Ratchford : *Journal of Physiology,* 1891, vol. 12, p. 27.

started by a stimulus of some kind. According to Röhmann,[1] it varies in quantity in different parts of the small intestine, being very scanty in the upper part and more abundant in the lower. The intestinal secretion is a yellowish liquid with a strong alkaline reaction. The reaction is due to the presence of sodium carbonate, the quantity of which is about 0.25 to 0.50 per cent. The chemical composition of the secretion has not been satisfactorily determined, but its digestive action has been investigated with success. Upon proteids and fats it is said to have no specific action—that is, it contains neither a proteolytic nor a fat-splitting enzyme. The possible value of its sodium carbonate in aiding the emulsification of fats has been referred to in the preceding paragraph. Upon carbohydrates the secretion has an important action. In the first place, it has been shown that it contains an amylolytic enzyme which is more abundant in the upper than in the lower part of the intestine. This enzyme doubtless aids the amylopsin of the pancreatic secretion in converting starches to sugar (maltose) or sugar and dextrin. What is still more important, however, is the presence of inverting enzymes capable of converting cane-sugar (saccharose) into dextrose and levulose, and of a similar enzyme capable of changing maltose (or dextrin) to dextrose. Both of these effects are examples of the conversion of di-saccharides to mono-saccharides.

The di-saccharides of importance in digestion are cane-sugar, milk-sugar, and maltose. The first of these forms a common constituent of our daily diet; the second occurs always in milk; and the third, as we have seen, is the main end-product of the digestion of starches. These substances are all readily soluble, and we might expect that they would be absorbed directly into the blood without undergoing further change. As a matter of fact, however, it seems that they are first dissociated under the influence of the inverting enzymes into simpler mono-saccharide compounds, although in the case of lactose this statement is perhaps not entirely justified, our knowledge of the fate of this sugar during absorption being as yet quite incomplete. According to some authors, lactose is absorbed unchanged (see Chemical section). The general nature of this change is expressed in the three following reactions:

$$C_{12}H_{22}O_{11} + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6.$$
Maltose.   Dextrose.   Dextrose.

$$C_{12}H_{22}O_{11} + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6.$$
Cane-sugar.   Dextrose.   Levulose.

$$C_{12}H_{22}O_{11} + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6.$$
Lactose.   Dextrose.   Galactose.
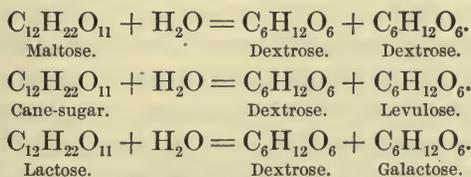
For the reactions by means of which these different isomeric forms of sugar are distinguished reference must be made to the Chemical section. The final stage in the artificial digestion of starches is the formation of maltose or of a mixture of maltose and dextrins. In the intestines, however, the process is carried a step farther by the aid of the inverting enzymes, and the maltose, and apparently the dextrins also, are converted into dextrose. According to this description, all of the starch is finally absorbed into the blood in the form of dextrose;

[1] *Pflüger's Archiv für die gesammte Physiologie*, 1887, vol. 41, p. 411.

and this conclusion falls in with the fact that the sugar found normally in the blood exists always in the form of dextrose. With reference to the inverting enzymes found in the small intestine, it should be added that they occur more abundantly in the mucous membrane than in the secretion itself. Indeed, the secretion is normally so scanty, especially in the upper part of the intestine, that it cannot be supposed to do more than moisten the free surface, and it is probable that the action of the inverting enzymes takes place upon or in the mucous membrane, as the last step in the series of digestive changes of the carbohydrates immediately preceding their absorption.

Digestion in the Large Intestine.—Observations upon the secretions of the large intestine have been made upon human beings in cases of anus præter-naturalis in which the lower portion of the intestine (rectum) was practically isolated. These observations, together with those made upon lower animals, unite in showing that the secretion of the large intestine is mainly composed of mucus, as the histology of the mucous membrane would indicate, and that it is very alkaline, and probably contains no digestive enzymes of its own. When the contents of the small intestine pass through the ileo-cæcal valve into the colon they still contain a quantity of incompletely digested material mixed with the enzymes of the small intestine. It is likely, therefore, that some at least of the digestive processes described above may keep on for a time in the large intestine ; but the changes here of most interest are the absorption which takes place and the bacterial decompositions. The latter are described briefly below.

Bacterial Decompositions in the Intestines.—Bacteria of different kinds have been found throughout the alimentary canal from the mouth to the rectum. In the stomach, however, under normal conditions, the strong acid reaction prevents the action of those putrefactive bacteria which decompose proteids, and prevents or greatly retards the action of those which set up fermentation in the carbohydrates. Under certain abnormal conditions known to us under the general term of *dyspepsia*, bacterial fermentation of the carbohydrates may be pronounced, but this must be considered as pathological.

In the small intestine the secretions are all alkaline, and it was formerly taken for granted that the intestinal contents are normally alkaline. If this were so the bacteria would find a favorable environment. It was supposed that putre-faction of the proteids must certainly occur, especially during the act of tryptic digestion, and this supposition was borne out by the extraordinary readiness of ar-tificial pancreatic digestions to undergo putrefaction when not protected in some way. Two recent cases [1] of fistula of the ileum at its junction with the colon in human beings have given opportunity for exact study of the contents of the small intestine. The results are interesting, and to a certain extent are opposed to the preconceived notions as to reaction and proteid putrefaction which have just been stated. They show that the contents of the intestine at the point where they are about to pass into the large intestine are acid, provided a mixed

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[1] Macfadyen, Nencki, and Sieber: *Archiv für expermentelle Pathologie u. Pharmakologie,* 1891, vol. 28, p. 311 ; Jakowski: *Archives des Sciences biologiques,* St. Petersburg, 1892, vol. 1.

diet is used, the acidity being due to organic acids (acetic) and being equal to 0.1 per cent. acetic acid. These acids must have come from the bacterial fermentation of the carbohydrates, and a number of bacteria capable of producing such fermentation were isolated. The products of bacterial putrefaction of the proteids, on the contrary, are absent, and it has been suggested that the acid reaction produced by the fermentation of the carbohydrates serves the useful purpose, under normal conditions, of preventing the putrefaction of the proteids. With reference, therefore, to the point we are discussing—namely, the bacterial decomposition of the contents of the intestines—we may conclude, upon the evidence furnished by these two cases, that in the human being, when living on a mixed diet, some of the carbohydrates undergo bacterial decomposition in the small intestine, but that the proteids are protected. We may further suppose that in the case of the proteids the limits of protection are easily overstepped, and that such a condition as a large excess of proteid in the diet or a deficient absorption from the small intestine may easily lead to extensive intestinal putrefaction involving the proteids as well as the carbohydrates.

In the large intestine, on the contrary, the alkaline reaction of the secretion is more than sufficient to neutralize the organic acids arising from fermentation of the carbohydrates, and the reaction of the contents is therefore alkaline. Here, then, what remains of the proteids undergoes, or may undergo, putrefaction, and this process must be looked upon as a normal occurrence in the large intestine. The extent of the bacterial action upon the proteids as well as the carbohydrates may vary widely even within the limits of health, and if excessive may lead to intestinal troubles. Among the products formed in this way, the following are known to occur: Leucin, tyrosin, and other amido-acids; indol; skatol; phenols; various members of the fatty-acid series, such as lactic, butyric, and caproic acids; sulphuretted hydrogen; methane; hydrogen; methyl mercaptan, etc. Some of these products will be described more fully in treating of the composition of the feces. To what extent these products are of value to the body it is difficult, with our imperfect knowledge, to say. It has been pointed out, on the one hand, that some of them (skatol, fatty acids, CO_2, CH_4, and H_2S) promote the movements of the intestine, and may be of value from this standpoint; on the other hand, some of them are absorbed into the blood, to be eliminated again in different form in the urine (indol and phenols), and it may be that they are of importance in the metabolism of the body; but concerning this our knowledge is deficient. On the whole, we must believe that the food in its passage through the alimentary canal is acted upon mainly by the digestive enzymes, the so-called "unorganized" ferments, but that the action of the bacteria, or organized ferments, is responsible for a part of the changes which the food undergoes before its final elimination in the form of feces. These two kinds of action vary greatly within normal limits, and to a certain extent they seem to be in inverse relationship to each other. When the digestive enzymes and secretions are deficient or ineffective the field of action for the bacteria is increased, and this seems to be the case in some pathological conditions, the result being intes-

tinal troubles of various kinds. The limits of normal bacterial action have not been worked out satisfactorily, but it is evident that our knowledge of digestion will not be complete until this is accomplished.

E. Absorption; Summary of Digestion and Absorption of the Food-stuffs; Feces.

In the preceding sections we have followed the action of the various digestive secretions upon the food-stuffs as far as the formation of the supposed end-products. In order that these products may be of actual nutritive value to the body, it is necessary, of course, that they shall be absorbed into the circulation and thus be distributed to the tissues. There are two possible routes for the absorbed products to take: they may pass immediately into the blood, or they may enter the lymphatic system, the so-called " lacteals " of the alimentary canal. In the latter case they reach the blood finally before being distributed to the tissues, since the thoracic duct, into which the lymphatics of the alimentary canal all empty, opens into the blood-vascular system at the junction of the left internal jugular and subclavian veins. The substances which take this route are distributed to the tissues by the blood, but it is to be noticed that, owing to the sluggish flow of the lymph-circulation (see section on Circulation), a relatively long time elapses after digestion before they enter the blood-current. The products which enter the blood directly from the alimentary canal are distributed rapidly; but in this case we must remember that they first pass through the liver, owing to the existence of the portal circulation, before they reach the general circulation. During this passage through the liver, as we shall find, changes of the greatest importance take place. The physiology of absorption is concerned with the physical and chemical means by which the end-products of digestion are taken up by the blood or the lymph, and the relative importance of the stomach, the small intestine, and the large intestine in this process. Leaving aside the fats, whose absorption is a special case, the absorption of the other products of digestion was formerly thought to be a simple physical process. The processes of osmosis, and to a lesser extent of filtration and imbibition, as they are known to occur outside the body, were supposed to account for the absorption of all the soluble products. This belief has now given way, in large part, to newer views, according to which the living epithelial cells take an active part in absorption, acting under laws peculiar to them as living substances, and different from the laws of diffusion, filtration, etc. established for dead membranes. Since, however, it is highly probable that osmosis plays a part in absorption, it will be convenient to give a brief definition of this process as it occurs outside the body, in order that the use made of it in explaining physiological absorption, as well as the objections to its use, may more easily be understood.

Diffusion and Osmosis.—Certain liquids when brought into contact with each other gradually mix, owing to the attraction of the molecules for each

other, giving finally a solution of uniform composition. The process of mixing —that is, of the passage of the molecules of one liquid into the intermolecular spaces of the other—is called "diffusion." Some liquids—water and oil, for example—will not diffuse with each other, or, as ordinarily stated, they are not miscible. When two miscible liquids are separated by a membrane, diffusion still takes place through the substance of the membrane; the process under these conditions is called "osmosis" or "dialysis," and it occurs independently of any difference of pressure on the two sides. It is well to bear in mind that, in order that osmosis may occur, it is not necessary that there should be actual capillary pores in the membrane. We may suppose such pores to be entirely absent, and yet osmosis be possible, since the liquids in this case, or one of them at least, may be imbibed into the substance of the membrane and thus be brought into contact. Imbibition, or the swelling of a membrane with water, is, in fact, always preliminary to the process of osmosis. When two liquids containing soluble constituents in different proportions are separated by a membrane, the tendency is for osmosis to occur until an equable composition is found on the two sides, diffusion equilibrium being established. This possibility cannot always be fulfilled, for the reason that some soluble substances do not undergo osmosis, or, as we usually say, are not dialyzable. As is well known, Graham separated soluble substances into two great classes—the *crystalloids*, comprising most of the crystalline bodies, which are dialyzable; and the *colloids*, such as gelatin, which are not dialyzable. The rapidity of osmosis of a crystalloid is measured by some form of osmometer. The simplest form consists of a glass tube the end of which is closed by a membrane—for example, a piece of parchment. If we place a strong solution of sodium chloride in such a tube and then bring the bottom of the membrane into contact with distilled water, diffusion will take place, sodium chloride passing through the parchment into the distilled water outside (exosmosis), and water passing back into the tube (endosmosis). The weight of water which passes into the salt solution is much greater than the weight of salt which passes into the distilled water. If the process is allowed to go on long enough, the proportion of sodium chloride outside and inside will be the same, but the volume of liquid inside the osmometer will be increased greatly. In an experiment of this character it is not difficult to determine what weight of water passes one way through the membrane for a given unit (1 gram) of the crystalloid passing the other way. On the supposition that this ratio is constant, it was determined for a number of crystalloids, and represents what is known as the "endosmotic equivalent," $\frac{water}{salt}$. As a matter of fact, the ratio is not constant: it varies among other things with the strength of solutions used. Still the term is often used; and it is a convenient one, as it expresses the approximate rate of dialysis of different substances. Colloidal substances, such as albumin solutions, which dialyze very slightly, have been supposed to have a high osmotic equivalent, but so far at least as the proteids are concerned this seems to be an error. Recent work has shown that these bodies exert only a slight attraction for water.[1]

[1] See Heidenhain : *Pflüger's Archiv für die gesammte Physiologie,* 1894, Bd. lvi. S. 637.

From this brief description it will be seen that osmosis supposes the existence of two miscible liquids lying on opposite sides of a membrane. In the alimentary canal we have this arrangement. The mucous membrane represents the dialyzing membrane; on one side is the blood or the lymph, and on the other side are the contents of the stomach or the intestine. If in the latter there is more sugar, let us say, than in the blood, then, according to the principles of osmosis, the sugar will tend to dialyze through the mucous membrane into the blood, and a quantity of water corresponding to its endosmotic equivalent will pass back into the canal. The fact that the blood is in rapid movement should promote the rapidity of dialysis, for the obvious reason that it tends to prevent an equalization in composition; just as in ordinary osmosis, if the parchment tube containing the substance to be dialyzed is swung in running water, the osmosis will be more complete and more rapid than when it is suspended in a given bulk of water which is not changed.

With this brief exposition of the meaning of the terms *diffusion*, *osmosis*, and *dialysis*, let us pass on first to a consideration of the facts known with reference to the actual absorption that occurs in different parts of the alimentary canal.

Absorption in the Stomach.—In the stomach it is possible that there might be absorption of the following substances: water; salts; sugars and dextrins, which may have been formed in salivary digestion from starch, or which may have been eaten as such; the proteoses and peptones formed in the peptic digestion of proteids or albuminoids. In addition, absorption of soluble or liquid substances—drugs, alcohol, etc.—which have been swallowed may occur. It was formerly assumed without definite proof that the absorption in the stomach of such things as water, salts, sugars, and peptones was very important. Of late years a number of actual experiments have been made, under conditions as nearly normal as possible, to determine the extent of absorption in this organ. These experiments have given unexpected results, showing, upon the whole, that absorption does not take place readily in the stomach—certainly nothing like so easily as in the intestine. The methods made use of in these experiments have varied, but the most interesting results have been obtained by establishing a fistula of the duodenum just beyond the pylorus.[1] Through a fistula in this position substances can be introduced into the stomach, and if the cardiac orifice is at the same time shut off by a ligature or a small balloon, they can be kept in the stomach a given time, then be removed, and the changes, if any, be noted. After establishing the fistula in the duodenum food may be given to the animal, and the contents of the stomach as they pass out through the fistula may be caught and examined. The older methods of introducing the substance to be observed into the stomach through the œsophagus or through a gastric fistula were of little use, since, if the substance disappeared, there was no way of deciding whether it was absorbed or was simply passed on into the intestine.

[1] Compare V. Mering: *Ueber die Function des Magens*, 1893; Edkins: *Journal of Physiology*, 1892, vol. 13, p. 445; Brandl: *Zeitschrift für Biologie*, 1892, vol. 29, p. 277.

Water.—Experiments of the character just described show that water when taken alone is practically not absorbed at all in the stomach. Von Mering's experiments especially show that as soon as water is introduced into the stomach it begins to pass out into the intestine, being forced out in a series of spirts by the contractions of the stomach. Within a comparatively short time practically all the water can be recovered in this way, none or very little having been absorbed in the stomach. For example, in a large dog with a fistula in the duodenum, 500 cubic centimeters of water were given through the mouth. Within twenty-five minutes 495 cubic centimeters had been forced out of the stomach through the duodenal fistula. The result was not true for all liquids; alcohol, for example, was absorbed readily.

Salts.—The absorption of salts from the stomach has not been investigated thoroughly. According to Brandl, sodium iodide is absorbed very slowly or not at all in dilute solutions. Not until its solutions reach a concentration of 3 per cent. or more does its absorption become important. This result, if applicable to all the soluble inorganic salts, would indicate that under ordinary conditions they are practically not absorbed in the stomach, since it cannot be supposed that they are normally swallowed in solutions so concentrated as 3 per cent. It was found that the absorption of sodium iodide was very much facilitated by the use of condiments, such as mustard and pepper, or alcohol, which act either by causing a greater congestion of the mucous membrane or perhaps by directly stimulating the epithelial cells.

Sugars and Peptones.—Experiments by the newer methods leave no doubt that sugars and peptones can be absorbed from the stomach. In Von Mering's work different forms of sugar—dextrose, lactose, saccharose (cane-sugar), maltose, and also dextrin—were tested. They were all absorbed, but it was found that absorption was more marked the more concentrated were the solutions. Brandl, however, reports that sugar (dextrose) and peptone were not sensibly absorbed until the concentration had reached 5 per cent. With these substances also the ingestion of condiments or of alcohol increased distinctly the absorptive processes in the stomach. On the whole it would seem that sugars and peptones are absorbed with some difficulty from the stomach.

Fats.—As we have seen, fats undergo no digestive changes in the stomach. The process of emulsification is supposed to be a necessary preliminary step to absorption, and, as this process takes place only after the fats have reached the small intestine, there seems to be no doubt that in the stomach fats escape absorption entirely.

Absorption in the Small Intestine.—The soluble products of digestion —sugars and peptones or proteoses, as well as the emulsified fats—are mainly absorbed in the small intestine. This we should expect from a mere *a priori* consideration of the conditions prevailing in this part of the alimentary canal. The partially-digested food sent out from the stomach meets the digestive secretions in the beginning of the small intestine. As we have seen, the different enzymes of the pancreatic secretion act powerfully upon the three important classes of food-stuffs, and we have every reason to believe that their digestion

makes rapid progress. The passage of the food along the small intestine, although rapid compared with its passage through the large intestine, requires a number of hours for its completion. According to the observations made upon a patient with a fistula at the end of the small intestine,[1] food begins to pass into the large intestine in from two to five and a quarter hours after it has been eaten, and it requires from nine to twenty-three hours before the last portions reach the end of the small intestine; this estimate includes, of course, the time in the stomach. During this progress it has been converted for the most part into a condition suitable for absorption, and the mucous membrane with which it is in contact is one peculiarly adapted for absorption, since its epithelial surface is greatly increased in extent by the vast number of villi as well as by the numerous large folds known as the " valvulæ conniventes." In addition to these considerations, however, we have abundant experimental proof that absorption takes place actively in the small intestine. The absorption of fats can be demonstrated microscopically, as will be described presently. Experiments made by Röhmann[2] and others with isolated loops of intestine have shown that sugars and peptones are absorbed readily and in much more dilute solutions than in the stomach. Moreover, in the case just referred to, of an intestinal fistula at the end of the small intestine, a determination of the proteid present in the discharge from the fistula, after a test-meal containing a known amount of proteid, showed that about 85 per cent. had disappeared —that is, had been absorbed before reaching the large intestine. With reference to water and salts, it has been shown that they also are readily absorbed; some very interesting experiments demonstrating this fact have been reported recently by Heidenhain in a paper which is referred to briefly on page 95. It must be remembered, however, that under normal conditions the absorption of water and salts is more or less compensated by the secretion formed along the length of the intestine, so that when the contents reach the ileo-cæcal valve they are still of a fluid consistency similar to that of the chyme as it left the stomach to enter the intestine. A consideration of the mechanism of the absorption of fats, sugars, peptones, and water will be taken up presently, after a few words have been said of absorption in the large intestine.

Absorption in the Large Intestine.—There can be no doubt that absorption forms an important part of the function of the large intestine. The contents pass through it with great slowness, the average duration being given usually as twelve hours, and while they enter through the ileo-cæcal valve in a thin fluid condition, they leave the rectum in the form of nearly solid feces. This fact alone demonstrates the extent of the absorption of water. As for the sugar and peptones, examination of the intestinal contents as they entered the large intestine in the case of fistula cited in the preceding paragraph showed that there may still be present an important percentage of proteid (14 per cent.) and a variable amount of sugars and fats—more than is

[1] Macfadyen, Nencki, and Sieber: *Archiv für experimentelle Pathologie u. Pharmakologie*, 1891, vol. 28, p. 311.

[2] *Pflüger's Archiv für die gesammte Physiologie*, 1887, vol. 41, p. 411.

found normally in the feces. Some of this carbohydrate and proteid undergoes destruction by bacterial action, as has already been explained (p. 249), but some of it is absorbed, or may be absorbed, before decomposition occurs. The power of absorption in the large intestine has been strikingly demonstrated by the fact that various substances injected into the rectum are absorbed and suffice to nourish the animal. Enemata of this character are frequently used in medical practice with satisfactory results, and careful experimental work on lower animals and on men under conditions capable of being properly controlled has corroborated the results of medical experience and shown that even in the rectum absorption takes place. Without giving the details of this work, it may be said that it is now known that proteids in solution, or even such things as eggs beaten to a fluid mass with a little salt, are absorbed from the rectum, and this notwithstanding the fact that no proteolytic enzyme is found in this part of the alimentary canal. The theoretical bearing of this fact upon the general process of absorption will be brought out in the next paragraph. Fats also (such as milk-fat) and sugars can be absorbed in the same way.

Absorption of Proteids.—As we have seen in the preceding paragraphs, absorption of proteids takes place in the stomach and the small and large intestines, but in all probability mainly in the small intestine. The end-products of the digestion of proteids by the proteolytic enzymes are proteoses and peptones. Tryptic digestion produces also leucin, tyrosin, and the related amido- bodies, but so far as proteid has undergone decomposition to this stage it is no longer proteid, and does not have the nutritive value of proteid. The logical conclusion from our knowledge of proteid digestion should be that all proteid is reduced to the form of proteoses or peptones before absorption, and that the great advantage of proteolysis is that proteids are more readily absorbed in this form than in any other. In the main we must accept this conclusion. The process of proteid digestion would seem to be without meaning otherwise. But we must not shut our eyes to the fact that proteid may be absorbed in other forms than peptones or proteoses. This has been demonstrated most clearly for the rectum and the lower part of the colon, as was stated in the preceding paragraph. Enemata of dissolved muscle-proteid (myosin), egg-albumin, etc. are absorbed from this part of the alimentary canal without, so far as can be determined, previous conversion to peptones and proteoses, and we must admit that the same power is possessed by other parts of the intestinal tract. It is probable, for instance, that the very first product of pepsin-hydrochloric digestion, syntonin, is capable of absorption directly. This fact, however, does not weaken the conclusion that peptones and proteoses are absorbed more easily than other forms of proteids, and that they constitute the form in which the bulk of our proteid is absorbed. Opinions as to why these forms of proteids are more easily absorbed than any other must vary with the theory held as to the nature of absorption. It was formerly believed that absorption is entirely a process of imbibition and osmosis through the mucous membrane. The fact that proteoses and peptones

are more easily diffusible than are other forms of proteids harmonized with this theory. The object of digestion, it was said, is to convert the insoluble and non-dialyzable proteids into soluble, diffusible peptones. But a study of the details of proteid absorption has shown that the process cannot be explained by the laws of simple dialysis which govern the process of diffusion through dead membranes. Proteids, like egg-albumin, which are practically non-dialyzable are absorbed readily from the intestine. Moreover, when one considers the rate of absorption of peptone from the alimentary tract, it seems to be much too rapid and complete to be accounted for entirely by the diffusibility of this substance as determined by experiments with parchment dialyzers. It is believed, therefore, that the initial act in the absorption of proteids is dependent in some way upon the properties of the living epithelial cells lining the mucous membrane. It is impossible at present to make this statement more specific. A second similar suggestion attributes the absorption of proteids to the leucocytes found so abundantly in the adenoid tissue of the intestine, but this has been shown by Heidenhain[1] and others to be incorrect. We say, then, in brief, that the peptones and proteoses are absorbed by a special activity of the epithelial cells. Are they then transferred to the blood or to the lymph? Experiments have shown conclusively that they are transmitted directly to the blood-capillaries: ligature of the thoracic duct, for example, which shuts off the entire lymph-flow coming from the intestine, does not interfere with the absorption of proteids. There is one other fact of great significance in connection with this subject: the proteids are absorbed mainly, if not entirely, as proteoses and peptones, and they pass immediately into the blood; nevertheless, examination of the blood directly after eating, while the process of absorption is in full activity, fails to show any peptones or proteoses in the blood. In fact, if these substances are injected directly into the blood, they behave as foreign, and even as toxic, bodies. In certain doses they produce insensibility with lowered blood-pressure, and they may bring on a condition of coma ending in death. Moreover, when present in the blood, even in small quantities, they are eliminated by the kidneys and are evidently unfit for the use of the tissues. It follows from these facts that while the peptones and proteoses are being absorbed by the epithelial cells they are at the same time changed into some other form of proteid. What this change is has not been determined. Experiments have shown that peptones disappear when brought into contact with fresh pieces of the lining mucous membrane of the intestine which are still in a living condition. The presumption is that the peptones and proteoses are converted to serum-albumin, or at least to a native albumin of some kind, but we have no definite knowledge beyond the fact that the peptones and proteoses, as such, disappear. It is well to call attention to the fact that the digestion of proteids is supposed, according to the schema already described, to consist in a process of hydration and splitting, with the formation, probably, of smaller molecules. The reverse act of conversion of peptones back to albu-

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[1] *Pflüger's Archiv für die gesammte Physiologie*, vol. 43, 1888, supplement.

miu implies, therefore, a process of dehydration and polymerization which presumably takes place in the epithelial cells. It is at this point in the act of absorption of proteids that our knowledge is most deficient.

Absorption of Sugars.—The carbohydrates are absorbed mainly in the form of sugar or of sugar and dextrin. Starches are converted in the intestine into maltose or maltose and dextrin, and then by the inverting enzymes of the mucous membrane are changed to dextrose. Ordinary cane-sugar suffers inversion into dextrose and levulose before absorption, and milk-sugar possibly undergoes a similar inversion into dextrose and galactose, though less is known of this. So far as our knowledge goes, then, we may say that the carbohydrates of our food are eventually absorbed in the form mainly of dextrose or of dextrose and levulose, leaving out of consideration, of course, the small part that normally undergoes bacterial fermentation. In accordance with this statement, we find that the sugar of the blood exists in the form of dextrose. It is apparently a form of sugar that can be oxidized very readily by the tissues. In fact, it has been shown that if cane-sugar is injected directly into the blood, it cannot be utilized, at least not readily, by the tissues, since it is eliminated in the urine ; whereas if dextrose is introduced directly into the circulation, it is all consumed, provided it is not injected too rapidly. The sugars are soluble and dialyzable, but, as in the case of peptones, exact study of their absorption shows that it does not follow the known laws of osmosis. The degree of absorption of the different sugars does not vary directly with their diffusibility. Moreover in the small intestine at least the rate of absorption increases with the concentration of the solution only up to a certain point (with dextrose, 5 to 6 per cent.) at which the maximum of absorption takes place, whereas, if it were simply a case of osmosis, the rapidity of diffusion ought to increase with an increase in concentration of the solution on one side of the membrane. For these and for other reasons it seems that the absorption of sugars is also a special act depending, in all probability, upon the living epithelial cells. Their absorption seems to be effected by means similar to those used for the proteids, but the details of the act cannot be given. As in the case of the proteids, the absorbed sugars—dextrose or dextrose and levulose—pass directly into the blood, and do not under normal conditions enter the lymph-vessels. This has been demonstrated by direct examination of the blood of the portal vein during digestion (Von Mering [1]), a distinct increase in its sugar-contents being found. Examination of the lymph shows no increase in sugar unless excessive amounts of carbohydrates have been eaten (Heidenhain).

Absorption of Fats.—Unlike the sugars and peptones, fats are absorbed chiefly in a solid form—that is, in an emulsified condition. There can be no question therefore, in this case, of osmosis ; the process of absorption must be of a mechanical nature. The details of the process have been worked out microscopically and have given rise to numerous researches. It is unnecessary to speak of the various theories that have been held, as it has been shown by

[1] Du Bois-Reymond's *Archiv für Anatomie und Physiologie,* 1877, p. 413.

nearly all the recent work that the immediate agent in the absorption of fats is again the epithelial cells of the villi of the small intestine. The fat-droplets are taken up by these cells, and can be seen microscopically after digestion in the act of passing, or rather of being passed, through the cell-substance. The epithelial cells, in other words, ingest the fat-particles lying against their free ends, and then pass them slowly through their cytoplasm, forcing them finally out of the basal end of the cells into the substance, the stroma, of the villus. Reference to the histology of the villi will show that each villus possesses a comparatively large lymphatic capillary lying in its middle and ending blindly, apparently, near the apex of the villus. Between this central lymphatic—or lacteal, as it is called here—and the epithelium lies the stroma, or main substance of the villus, which, in addition to its blood-capillaries and plain muscle-fibres, consists mainly of lymphoid or adenoid tissue containing numerous leucocytes. The fat-droplets have to pass from the epithelium to the central lymphatic, for it is one of the most certain facts in absorption, and one which has been long known, that the fat absorbed in an emulsified condition gets eventually into the lacteals and thence is conveyed through the system of lymphatic vessels to the thoracic duct and finally to the blood. The name " lacteal," in fact, is given to the lymphatic capillaries of the villus on account of the milky appearance of their contents, after meals, caused by the emulsified fat. It should be added, however, that it has not been possible to demonstrate experimentally that all the absorbed fat passes into the thoracic duct. Attempts have been made to collect all the fat passing through the thoracic duct after a meal containing a known quantity of fat, but even after making allowance for the unabsorbed fat in the feces there is a considerable percentage of the fat absorbed which cannot be recovered from the lymph of the thoracic duct. While this result does not invalidate the conclusion stated above that the emulsified fat passes chiefly, perhaps entirely, into the lacteals, it does indicate that there are some factors concerned in the process of fat-absorption which are at present unknown to us. The passage of the fat-droplets to the central lacteal is not difficult to understand. The adenoid tissue of the stroma is penetrated by minute unformed lymph-channels which are doubtless connected with the central lacteal. In each villus lymph is continually formed from the circulating blood, so that there must be a slow stream of lymph through the stroma to the lacteal. When the fat-droplets have passed through the epithelial cells (and basement membrane) they drop into the interstices of the adenoid tissue and are carried in this stream into the lacteal. The lacteals were formerly designated as the " absorbents," under the false impression that they attended to all the absorption going on in the intestines, including that of peptones, sugars, and fats. It is now known that their action under ordinary conditions is limited to the absorption of fats.

Absorption of Water and Salts.—From what has been said (p. 252) it is evident that absorption of water takes place very slightly, if at all, in the stomach. Whenever soluble substances, such as peptones, sugars, or salts, are absorbed in this organ, a certain amount of water must go with them, but the

bulk of the water passes out of the pylorus. In the small intestine absorption of water and of inorganic salts evidently takes place readily, and, according to the experiments of Röhmann and Heidenhain already referred to, the laws governing their absorption are different from what we should expect if the process were simply one of osmosis. The differences as regards the absorption of salts are especially emphasized by the experiments of Heidenhain.[1] Making use of an interesting method, for which reference must be made to the original paper, Heidenhain has shown that if dilute solutions of NaCl (0.3 to 0.5 per cent.) are introduced into an isolated loop of the small intestine, absorption of both water and salts takes place readily, in spite of the fact that in this case the blood is the more concentrated solution and has therefore the greater osmotic pressure. Moreover, specimens of the animal's own blood-serum introduced into an intestinal loop are also completely absorbed, although in this case there is practically no difference in composition, as regards water and salts, between the blood of the animal and the serum introduced into the intestine. In another paper by Heidenhain[2] he proved that the absorption of water in the small intestine, when ordinary amounts are ingested, takes place entirely through the blood-vessels of the villus, and not through the lacteals; when larger quantities of water are swallowed, a small part may be absorbed through the lacteals, as shown by the increased lymph-flow, but by far the larger quantity is taken up directly by the blood.

In the large intestine the contents become progressively more solid as they approach the rectum; the absorption of water is such that the stream is mainly from the intestinal contents to the blood, giving us a phenomenon somewhat similar to the absorption of water by the roots of a plant. This process is difficult to understand upon the supposition that it is caused by osmosis, using that term in its ordinary sense. We must suppose an active attraction of a peculiar character for water on the part of some substance in the epithelial cells of the wall of the large intestine.

Composition of the Feces.—The feces differ widely in amount and in composition with the character of the food. Upon a diet composed exclusively of meats they are small in amount and dark in color; with an ordinary mixed diet the amount is increased, and it is largest with an exclusively vegetable diet. The average weight of the feces in twenty-four hours upon a mixed diet is given as 170 grams, while with a vegetable diet it may amount to as much as 400 or 500 grams. The quantitative composition, therefore, will vary greatly with the diet. Qualitatively, we find in the feces the following things: (1) Indigestible material, such as ligaments of meat or cellulose from vegetables. (2) Undigested material, such as fragments of meat, starch, or fats which have in some way escaped digestion. Naturally, the quantity of this material present is slight under normal conditions. Some fats, however, are almost always found in feces, either as neutral fats or as fatty acids, and to a small extent as calcium or magnesium soaps. The quantity of fat found is

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[1] *Pflüger's Archiv für die gesammte Physiologie*, 1894, vol. 56, p. 579.
[2] *Ibid.*, vol. 43, 1888, supplement.

increased by an increase of the fats in the food. (3) Products of bacterial decomposition. The most characteristic of these products are indol and skatol. These two substances are formed normally in the large intestine from the putrefaction of proteid material. They occur always together. Indol has the formula C_8H_7N, and skatol, which is a methyl indol, the formula C_9H_9N. They are crystalline bodies possessing a disagreeble fecal odor; this is espe-ially true of skatol, to which the odor of the feces is mainly due. Indol and skatol are eliminated from the body only in part in the feces; a certain propor-portion of each is absorbed into the blood and is eliminated in a modified form through the urine—indol as indican (indoxyl-sulphuric acid), from which indigo was formerly made, and skatol as skatoxyl-sulphuric acid (see Chemical section for further information as to the chemistry of these bodies). (4) Cholesterin, which is found always in small amounts and is probably derived from the bile. (5) Excretin, a crystallizable, non-nitrogenous substance to which the formula $C_{78}H_{156}SO_2$ has been assigned, is found in minute quantities. (6) Mucus and epithelial cells thrown off from the intestinal wall. (7) Pigment. In addition to the color due to the undigested food or to the metallic compounds contained in it, there is normally present in the feces a pigment, hydrobilirubin, derived from the pigments (bilirubin) of the bile. Hydrobilirubin is formed from the bilirubin by reduction in the intestine. (8) Inorganic salts—salts of sodium, potassium, calcium, magnesium, and iron. The importance of the calcium and iron salts will be referred to again in a subsequent chapter, when speaking of their nutritive importance. (9) Micro-organisms. Great quantities of bac-teria of different kinds are found in the feces.

In addition to the feces, there is found often in the large intestine a quantity of gas which may also be eliminated through the rectum. This gas varies in composition. The following constituents have been determined to occur at one time or another: CH_4, CO_2, H, N, H_2S. They arise mainly from the bacterial fermentation of the proteids, although some of the N may be derived from air swallowed with the food.

F. Physiology of the Liver and the Spleen.

The liver plays an important part in the general nutrition of the body; its functions are manifold, but in the long run they depend upon the properties of the liver-cell, which constitutes the anatomical and physiological unit of the organ. These cells are seemingly uniform in structure throughout the whole substance of the liver, but to understand clearly the different functions they fulfil one must have a clear idea of their anatomical relations to one another and to the blood-vessels, the lymphatics, and the bile-ducts. The histology of the liver lobule, and the relationship of the portal vein, the hepatic artery, and the bile-duct to the lobule, must be obtained from the text-books upon histol-ogy and anatomy. It is sufficient here to recall the fact that each lobule is supplied with blood coming in part from the portal vein and in part from the hepatic artery. The blood from the former source contains the soluble prod-ucts absorbed from the alimentary canal, such as sugar and proteid, and these

absorbed products are submitted to the metabolic activity of the liver-cells before reaching the general circulation. The hepatic artery brings to the liver-cells the arterialized blood sent out into the systemic circulation from the left ventricle. In addition, each lobule gives origin to the bile-capillaries which arise between the separate cells and which carry off the bile formed within the cells. In accordance with these facts, the physiology of the liver-cell falls naturally into two parts—one treating of the formation, composition, and physiological significance of bile, and the other dealing with the metabolic changes produced in the mixed blood of the portal vein and the hepatic artery as it flows through the lobules. In this latter division the main phenomena to be studied are the formation of *urea* and the formation and significance of *glycogen*.

Bile.—From a physiological standpoint, bile is partly an excretion carrying off certain waste products, and partly a digestive secretion playing an important rôle in the absorption of fats, and possibly in other ways. Bile is a continuous secretion, but in animals possessing a gall-bladder its ejection into the duodenum is intermittent. For the details of the mechanism of its secretion, its dependence on nerve- and blood-supply, etc., the reader is referred to the section on Secretion. Bile is easily obtained from living animals by establishing a fistula of the bile-duct or, as seems preferable, of the gall-bladder. The latter operation has been performed a number of times on human beings. In some cases the entire supply of bile has been diverted in this way to the exterior, and it is an interesting physiological fact that such patients may continue to enjoy good health, showing that, whatever part the bile takes normally in digestion and absorption, its passage into the intestine is not absolutely necessary to the nutrition of the body. The quantity of bile secreted during the day has been estimated for human beings of average weight (43 to 73 kilograms) as varying between 600 and 850 cubic centimeters. This estimate is based upon observations on cases of biliary fistula.[1] Chemical analyses of the bile show that, in addition to the water and salts, it contains bile-pigments, bile-acids, cholesterin, lecithin, neutral fats and soaps, sometimes a trace of urea, and a mucilaginous nucleo-albumin formerly designated improperly as *mucin*. The last-mentioned substance is not formed in the liver-cells, but is added to the bile by the mucous membrane of the bile-ducts and gall-bladder. The quantity of these substances present in the bile must vary greatly in different animals and under different conditions. As an illustration of their relative importance in human bile and of the limits of variation the two following analyses by Hammarsten[2] may be quoted:

	I.	II.
Solids	2.520	2.840
Water	97.480	97.160
Mucin and pigment	0.529	0.910
Bile-salts	0.931	0.814
Taurocholate	0.3034	0.053

[1] Copeman and Winston : *Journal of Physiology*, 1889, vol. x. p. 213; and Robson: *Proceedings of the Royal Society*, London, 1890, vol. 47, p. 499.

[2] Reported in *Centralblatt für Physiologie*, 1894, No. 8.

	I.	II.
Glycocholate	0.6276	0.761
Fatty acids from soap	0.1230	0.024
Cholesterin	0.0630	0.096
Lecithin ⎱ Fat ⎰	0.0220	0.1286
Soluble salts	0.8070	0.8051
Insoluble salts	0.0250	0.0411

The color of bile varies in different animals according to the preponderance of one or the other of the main bile-pigments, *bilirubin* and *biliverdin*. The bile of carnivorous animals has usually a bright golden color, owing to the presence of bilirubin, while that of the herbivora is a bright green from the biliverdin. The color of human bile seems to vary: according to some authorities, it is yellow or brownish yellow, and this seems especially true of the bile as found in the gall-bladder of the cadaver: according to others, it is of a dark-olive color with the greenish tint predominating. Its reaction is feebly alkaline and its specific gravity varies in human bile from 1050 or 1040 to 1010. Human bile does not give an absorption spectrum, but the bile of some herbivora, after exposure to the air at least, gives a characteristic spectrum. The individual constituents of the bile will now be described more in detail, but with reference mainly to their origin, fate, and function in the body. For a description of their strictly chemical properties and reactions reference must be made to the Chemical section.

Bile-pigments.—Bile, according to the animal from which it is obtained, contains one or the other, or a mixture, of the two pigments *bilirubin* and *biliverdin*. Biliverdin is supposed to stand to bilirubin in the relation of an oxidation product. Bilirubin is given the formula $C_{32}H_{36}N_4O_6$, and biliverdin $C_{32}H_{36}N_4O_8$, the latter being prepared readily from pure specimens of the former by oxidation. These pigments give a characteristic reaction, known as "Gmelin's reaction," with nitric acid containing some nitrous acid (nitric acid with a yellow color). If a drop of bile and a drop of nitric acid are brought into contact, the former undergoes a succession of color changes, the order being green, blue, violet, red, and reddish yellow. The play of colors is due to successive oxidations of the bile-pigments; starting with bilirubin, the first stage (green) is due to the formation of biliverdin. The pigments formed in some of the other stages have been isolated and named. The reaction is very delicate, and it is often used to detect the presence of bile-pigments in other liquids—urine, for example. The bile-pigments originate from hæmoglobin. This origin was first indicated by the fact that in old blood-clots or in extravasations there was found a crystalline product, the so-called "hæmatoidin," which was undoubtedly derived from hæmoglobin, and which upon more careful examination was proved to be identical with bilirubin. This origin, which has since been made probable by other reactions, is now universally accepted. It is supposed that when the blood-corpuscles go to pieces in the circulation (p. 343) the hæmoglobin is brought to the liver, and then, under the influence of the liver-cells, is converted to an

iron-free compound, bilirubin or biliverdin. It is very significant to find that the iron separated by this means from the hæmoglobin is for the most part retained in the liver, a small portion only being secreted in the bile. It seems probable that the iron held back in the liver is again used in some way to make new hæmoglobin in the hæmatopoietic organs. The bile-pigments are carried in the bile to the duodenum and are mixed with the food in its long passage through the intestine. Under normal conditions neither bilirubin nor biliverdin is found in the feces, but in their place is found a reduction product, *hydrobilirubin.* Moreover, it is believed that some of the bile-pigment is reabsorbed as it passes along the intestine, is carried to the liver in the portal blood, and is again eliminated. That this action occurs, or may occur, has been made probable by experiments of Wertheimer[1] on dogs. It happens that sheep's bile contains a pigment (cholohæmatin) which gives a characteristic spectrum. If some of this pigment is injected into the mesenteric veins of a dog, it is eliminated while passing through the liver, and can be recognized unchanged in the bile. The value of this " circulation of the bile," so far as the pigments are concerned, is not apparent.

Bile-acids.—" Bile-acids " is the name given to two organic acids, *glycocholic* and *taurocholic*, which are always present in bile, and, indeed, form very important constituents of that secretion ; they occur in the form of their respective sodium salts, and not as uncombined acids, as the term " bile-acids " might lead one to believe. In human bile both acids are usually found, but the proportion of taurocholate is variable, and in some cases this latter acid may be absent altogether. Among herbivora the glycocholate predominates as a rule, although there are some exceptions ; among the carnivora, on the other hand, taurocholate occurs usually in greater quantities, and in the dog's bile it is present alone. Glycocholic acid has the formula $C_{26}H_{43}NO_6$, and taurocholic acid has the formula $C_{26}H_{45}NSO_7$. Each of them can be obtained in the form of crystals. When boiled with acids or alkalies these acids take up water and undergo hydrolytic cleavage, the reaction being represented by the following equations :

$$C_{26}H_{43}NO_6 \ + \ H_2O \ = \ C_{24}H_{40}O_5 \ + \ CH_2(NH_2)COOH.$$
Glycocholic acid.   Cholic acid.   Glycocoll (amido-acetic acid).

$$C_{26}H_{45}NSO_7 + \ H_2O \ = \ C_{24}H_{40}O_5 \ + \ C_2H_7NSO_3.$$
Taurocholic acid.   Cholic acid.   Taurin (amido-ethyl-sulphonic acid).
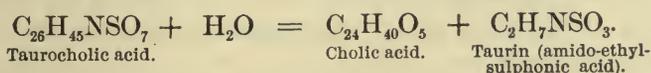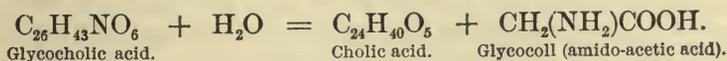
These reactions are interesting not only in that they throw light on the structure of the acids, but also because similar reactions doubtless take place in the intestine, cholic acid having been detected in the intestinal contents. As the formulas show, cholic acid is formed in the decomposition of each acid, and we may regard the bile-acids as compounds produced by the synthetic union of cholic acid with glycocoll in the one case and with taurin in the other. Cholic acid or its compounds, the bile-acids, are usually detected in suspected

[1] *Archives de Physiologie normale et pathologique*, 1892, p. 577.

liquids by the well-known Pettenkofer reaction. As usually performed, the test is made by adding to the liquid a few drops of a 10 per cent. solution of cane-sugar and then strong sulphuric acid. The latter must be added carefully and the temperature be kept below 70° C. If bile-acids are present, the liquid assumes a beautiful red-violet color. It is now known that the reaction consists in the formation of a substance (furfurol) by the action of the acid on sugar, which then reacts with the bile-acids. The bile-acids are formed directly in the liver-cells. This fact, which was for a long time the subject of discussion, has been demonstrated in recent years by an important series of researches made upon birds. It has been shown that if the bile-duct is ligated in these animals, the bile formed is reabsorbed and bile-acids and pigments may be detected in the urine and the blood. If, however, the liver is completely extirpated, then no trace of either bile-acids or bile-pigments can be found in the blood or the urine, showing that these substances are not formed elsewhere in the body than in the liver. It is more difficult to ascertain from what substances they are formed. The fact that glycocoll and taurin contain nitrogen, and that the latter contains sulphur, indicates that some proteid or albuminoid constituent is broken down during their production.

A circumstance of considerable physiological significance is that these acids or their decomposition products are absorbed in part from the intestine and are again secreted by the liver: as in the case of the pigments, there is an intestinal-hepatic circulation. The value of this reabsorption may lie in the fact that the bile-acids constitute a very efficient stimulus to the bile-secreting activity of the cells, being one of the best of cholagogues, or it may be that it economizes material. From what we know of the history of the bile-acids it is evident that they are not to be considered as excreta: they have some important function to fulfil. The following suggestions as to their value have been made: In the first place, they serve as a menstruum for dissolving the cholesterin which is constantly present in the bile and which is an excretion to be removed; secondly, they facilitate the absorption of fats from the intestine. The value of bile in fat-absorption will presently be referred to more in detail. It is an undoubted fact that when bile is shut off from the intestine the absorption of fats is very much diminished, and it has been shown that this action of the bile is owing to the presence of the bile-acids. In what way they act is unknown.

Cholesterin.—Cholesterin is a non-nitrogenous substance of the formula $C_{26}H_{44}O$. It is a constant constituent of the bile, although it occurs in variable quantities. Cholesterin is very widely distributed in the body, being found especially in the white matter (medullary substance) of nerve-fibres. It seems, moreover, to be a constant constituent of all animal and plant cells. It is assumed that cholesterin is not formed in the liver, but that it is eliminated by the liver-cells from the blood, which collects it from the various tissues of the body. That it is an excretion is indicated by the fact that it is eliminated unchanged in the feces. Cholesterin is insoluble in water or in dilute saline

liquids, and is held in solution in the bile by means of the bile-acids. We must regard it as a waste product of cell-life, formed probably in minute quantities, and excreted mainly through the liver. It is partly eliminated through the skin, in the sebaceous and sweat secretions, and in the milk.

Lecithin, Fats, and Nucleo-albumin.—*Lecithin* also seems to be present, generally in small quantities, in the cells of the various tissues, but it occurs especially in the white matter of nerve-fibres. It is probable, therefore, that, so far as it is found in the bile, it represents a waste product formed in different parts of the body and eliminated through the bile. The special importance, if any, of the small proportion of fats and fatty acids in the bile is unknown. The ropy, mucilaginous character of bile is due to the presence of a body formed in the bile-ducts and gall-bladder. This substance was formerly designated as *mucin*, but it is now known that in ox-bile at least it is not a true mucin, but is a *nucleo-albumin* (see Chemical section). Hammarsten reports that in human bile some true mucin is found. Outside the fact that it makes the bile viscous, this constituent is not known to possess any especial physiological significance.

General Physiological Importance of Bile.—The physiological value of bile has been referred to in speaking of its several constituents, but it will be convenient here to restate these facts and to add a few remarks of general interest. Bile is of importance as an excretion in that it removes from the body waste products of metabolism, such as cholesterin, lecithin, and bile-pigments. With reference to the pigments, there is evidence to show that a part at least may be reabsorbed while passing through the intestine, and be used again in some way in the body. The bile-acids represent end-products of metabolism involving the proteids of the liver-cells, but they are undoubtedly reabsorbed in part, and cannot be regarded merely as excreta. As a digestive secretion the most important function attributed to the bile is the part it takes in the digestion of fats. In the first place, it aids in the splitting of a part of the neutral fats and the subsequent emulsification of the remainder (p. 246). More than this, bile aids materially in the absorption of the emulsified fats. A number of observers have shown that when a permanent biliary fistula is made, and the bile is thus prevented from reaching the intestinal canal, a large proportion of the fat of the food escapes absorption and is found in the feces. This property of the bile is known to depend upon the bile-acids it contains, but how they act is not clearly understood. It was formerly believed, on the basis of some experiments by Von Westinghausen, that the bile-acids dissolve or mix with the fats and at the same time moisten the mucous membrane, and for these reasons aid in bringing the fat into immediate contact with the epithelial cells. It was stated, for instance, that oil rises higher in capillary tubes moistened with bile than in similar tubes moistened with water, and that oil will filter more readily through paper moistened with bile than through paper wet with water. Gröper,[1] who repeated these experiments, finds that they are erroneous. We must fall back,

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[1] *Archiv für Anatomie u. Physiologie* ("Physiol. Abtheilung"), 1889, p. 505.

therefore, upon the general statement that the bile-acids stimulate the epithe-lial cells to a greater activity in the absorption of fat, or possibly accomplish the same end in some more indirect way as yet undiscovered. It was formerly believed that bile is also of great importance in restraining the processes of putrefaction in the intestine. It was asserted that bile is an efficient antiseptic, and that this property comes into use normally in preventing excessive putre-faction. Bacteriological experiments made by a number of observers have shown, however, that bile itself has very feeble antiseptic properties, as is indicated by the fact that it putrefies readily. The free bile-acids and cholalic acid do have a direct retarding effect upon putrefactions outside the body; but this action is not very pronounced, and has not been demonstrated satis-factorily for bile itself. It seems to be generally true that in cases of biliary fistula the feces have a very fetid odor when meat and fat are taken in the food. But the increased putrefaction in these cases may possibly be due to some indirect result of the withdrawal of bile. It has been suggested, for instance, that the deficient absorption of fat which follows upon the removal of the bile results in the proteid and carbohydrate material becoming coated with an insoluble layer of fat, so that the penetration of the digestive enzymes is retarded and greater opportunity is given for the action of bacteria. We may conclude, therefore, that while there does not seem to be sufficient warrant at present for believing that the bile exerts a direct antiseptic action upon the intestinal contents, nevertheless its presence limits in some way the extent of putrefaction. Lastly, bile takes a direct part in suspending or destroying peptic digestion in the acid chyme forced from the stomach into the duodenum. The chyme meeting with bile and pancreatic juice is neutralized or is made alkaline, which alone would prevent further peptonization. Moreover, when chyme and bile are mixed a precipitate occurs, consisting partly of proteids (proteoses and syntonin) and partly of bile-acids. It is probable that pepsin, according to its well-known property, is thrown down in this flocculent pre-cipitate and, as it were, prepared for its destruction.

Glycogen.—One of the most important functions of the liver is the for-mation of *glycogen*. This substance was found in the liver in 1857 by Claude Bernard, and is one of several brilliant discoveries made by him. Glycogen has the formula $(C_6H_{10}O_5)_n$, which is also the general formula given to vegetable starch; glycogen is therefore frequently spoken of as "animal starch." It gives, however, a port-wine-red color with iodine solutions, instead of the familiar deep blue of vegetable starch, and this reaction serves to detect glyco-gen not only in its solutions, but also in the liver-cells. Glycogen is readily soluble in water, and the solutions have a characteristic opalescent appearance. Like starch, glycogen is acted upon by amylolytic enzymes, and the end-products are apparently the same—namely, maltose, or maltose and some dex-trin. For a more complete account of the chemical reactions of glycogen, and for the methods of obtaining it from the liver, reference must be made to the Chemical section.

Occurrence of Glycogen in the Liver.—Glycogen can be detected in

the liver-cells microscopically. If the liver of a dog is removed twelve or fourteen hours after a hearty meal, hardened in alcohol, and sectioned, the liver-cells will be found to contain clumps of clear material which give the iodine reaction for glycogen. Even when distinct aggregations of the glycogen cannot be made out, its presence in the cells is shown by the red reaction with iodine. By this simple method one can demonstrate the important fact that the amount of glycogen in the liver increases after meals and decreases again during the fasting hours, and if the fast is sufficiently prolonged it may disappear altogether. This fact is, however, shown more satisfactorily by quantitative determinations, by chemical means, of the total glycogen present. The amount of glycogen present in the liver is quite variable, being influenced by such conditions as the character and amount of the food, muscular exercise, body-temperature, drugs, etc. From determinations made upon various animals it may be said that the average amount lies between 1.5 and 4 per cent. of the weight of the liver. But this amount may be increased greatly by feeding upon a diet largely made up of carbohydrates. It is said that in the dog the total amount of liver-glycogen may be raised to 17 per cent., and in the rabbit to 27 per cent., by this means, while it is estimated for man (Neumeister) that the quantity may be increased to at least 10 per cent. It is usually believed that glycogen exists as such in the liver-cells, being deposited in the substance of the cytoplasm. Reasons have been brought forward recently to show that possibly this is not strictly true, but that the glycogen is held in some sort of weak chemical combination. It has been shown, for instance, that although glycogen is easily soluble in cold water, it cannot be extracted readily from the liver-cells by this agent. One must use hot water, salts of the heavy metals, and other similar means that may be supposed to break up the combination in which the glycogen exists. For practical purposes, however, we may speak of the glycogen as lying free in the liver-cells, just as we speak of hæmoglobin existing as such in the red corpuscles, although it is probably held in some sort of combination.

Origin of Glycogen.—To understand clearly the views held as to the origin of liver glycogen, it will be necessary to describe briefly the effect of the different food-stuffs upon its formation.

Effect of Carbohydrates on the Amount of Glycogen.—The amount of glycogen in the liver is affected very quickly by the quantity of carbohydrates in the food. If the carbohydrates are given in excess, the supply of glycogen may be increased largely beyond the average amount present, as has been stated above. Investigation of the different sugars has shown that dextrose, levulose, saccharose (cane-sugar), and maltose are unquestionably direct glycogen-formers, that is, that glycogen is formed directly from them or from the products into which they are converted during digestion. Now, our studies in digestion have shown that the starches are converted into maltose, or maltose and dextrin, during digestion, and, further, that these substances are changed or inverted to the simpler sugar dextrose during absorption. Cane-sugar, which forms such an important part of our diet, is inverted in the intestine into dextrose and

levulose, and is absorbed in this form. It is evident, therefore, that the bulk of our carbohydrate food reaches the liver as dextrose, or as dextrose and levulose, and these forms of sugar must be converted into glycogen in the liver-cells by a process of dehydration such as may be represented in substance by the formula $C_6H_{12}O_6 - H_2O = C_6H_{10}O_5$. In the case of levulose there is reason to believe that it is changed first to dextrose in the liver before being converted into glycogen. However that may be, there is no doubt that both dextrose and levulose increase markedly the amount of glycogen in the liver; and, since cane-sugar is inverted in the intestine before absorption, it also must be a good glycogen-former—a fact which has been abundantly demonstrated by direct experiment. Lusk[1] has shown, however, that if cane-sugar is injected under the skin, it has a very feeble effect in the way of increasing the amount of glycogen in the liver, since under these conditions it is probably absorbed into the blood without undergoing inversion. Experiments with subcutaneous injection of lactose gave similar results, and it is generally believed that the liver-cells cannot convert the double sugars to glycogen, at least not readily; hence the value of the inversion of these sugars in the alimentary canal before absorption. The relations of lactose to glycogen-formation have not been determined satisfactorily. If it contributes at all to the direct formation of glycogen, it is certainly less efficient than dextrose, levulose, or cane-sugar. When the proportion of lactose in the diet is much increased, it quickly begins to appear in the urine, showing that the limit of its consumption in the body is soon reached. This latter fact is somewhat singular, since in infancy especially milk-sugar forms a constant and important item of our diet, and one would suppose that it is especially adapted to the needs of the body.

Effect of Proteids on Glycogen-formation.—It was pointed out by Bernard, in his first studies upon glycogen-formation, that the liver can produce glycogen from proteid food. This conclusion has since been verified by more exact investigations. When an animal is fed upon a diet of proteid alone, or on proteid and gelatin, the carbohydrates being entirely excluded, glycogen is still formed in the liver, although in smaller amounts than in the case of carbohydrate foods. This is an important fact to remember in studying the metabolism of the proteids in the body, for, as glycogen is a carbohydrate and contains no nitrogen, it implies that the proteid molecule is dissociated into a nitrogenous and a non-nitrogenous part, the latter being converted to glycogen by the liver-cells. The possibility of the production of glycogen from proteids accords with a well-known fact in medical practice with reference to the pathological condition known as *diabetes.* In this disease sugar is excreted in the urine, sometimes in large quantities. As the sugar of the blood is formed from the carbohydrates in the food, it was thought that by excluding this food-stuff from the diet the excretion of sugar might be prevented. It has been found, however, that in some cases at least sugar continues to be present in the urine even upon a pure proteid diet. If we suppose that some of the proteid goes to form glycogen, the result observed is explained, for the gly-

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[1] Voit: *Zeitschrift für Biologie*, 1891, xxviii. p. 285.

cogen, as will be explained presently, is finally converted to sugar and is given off to the blood.

Effect of Fats and other Substances upon Glycogen-formation.—It has been found that fats take no part in the formation of liver glycogen. Glycerin increases the amount of glycogen in the liver, but the evidence goes to show that it is not a direct or an indirect glycogen-former. Glycerin seems to prevent the reconversion of glycogen to sugar by the liver-cells, and thus leads to an increased percentage of this substance in the liver.

The Function of Glycogen: Glycogenic Theory.—The meaning of the formation of glycogen in the liver has been, and still is, the subject of discussion. The view advanced first by Bernard is perhaps most generally accepted. According to Bernard, glycogen forms a temporary reserve supply of carbohydrate material which is laid up in the liver during digestion and which is gradually made use of in the intervals between meals. During digestion the carbohydrate food is absorbed into the blood of the portal system as dextrose or as dextrose and levulose. If these passed through the liver unchanged, the contents of the systemic blood in sugar would be increased perceptibly. It is now known that when the percentage of sugar in the blood rises above a certain low limit, the excess will be excreted through the kidney and will be lost. But as the blood from the digestive organs passes through the liver the excess of sugar is abstracted from the blood by the liver-cells, is dehydrated to make glycogen, and is retained in the cells in this form for a short period. From time to time the glycogen is reconverted into sugar (dextrose) and is given off to the blood. By this means the percentage of sugar in the systemic blood is kept nearly constant (0.1 to 0.2 per cent.) and within limits best adapted for the use of the tissues. The great importance of the formation of glycogen and the consequent conservation of the sugar-supply of the tissues will be more evident when we come to consider the nutritive value of carbohydrate food. Carbohydrates form the bulk of our usual diet, and the proper regulation of the supply to the tissues is therefore of vital importance in the maintenance of a normal healthy condition. The second part of this theory, which holds that the glycogen is reconverted to dextrose, is supported by observations upon livers removed from the body. It has been found that shortly after the removal of the liver the supply of glycogen begins to disappear and a corresponding increase in dextrose occurs. Within a comparatively short time all the glycogen is gone and only dextrose is found. It is for this reason that in the estimation of glycogen in the liver it is necessary to mince the organ and to throw it into boiling water as quickly as possible, since by this means the liver-cells are killed and the conversion of the glycogen is stopped. How the glycogen is changed to dextrose by the liver is a matter not fully explained. According to some, the conversion is due to an enzyme produced in the liver. Extracts of liver, as of many other organs, do contain a certain amount of an amylolytic enzyme, but this enzyme changes glycogen to maltose, whereas in the liver the glycogen is normally changed to dextrose. It is probable, therefore, that the conversion of glycogen to dextrose is dependent directly upon the

metabolic activity of the liver-cells, and so long as these cells are in a living condition they can effect this change. In this description of the origin and meaning of the liver glycogen reference has been made only to the glycogen derived directly from digested carbohydrates. The glycogen derived from proteid foods, once it is formed in the liver, has, of course, the same functions to fulfil. It is converted into sugar, and eventually is oxidized in the tissues. For the sake of completeness it may be well to add that some of the sugar of the blood formed from the glycogen may under certain conditions be converted into fat in the adipose tissues, instead of being burnt, and in this way it may be retained in the body as a reserve supply of food of a more stable character than is the glycogen.

Glycogen in the Muscles and other Tissues.—The history of glycogen is not complete without some reference to its occurrence in the muscles. Glycogen is, in fact, found in various places in the body, and is widely distributed throughout the animal kingdom. It occurs, for example, in leucocytes, in the placenta, in the rapidly-growing tissues of the embryo, and in considerable abundance in the oyster and other molluscs. But in our bodies and in those of the mammals generally the most significant occurrence of glycogen, outside of the liver, is in the voluntary muscles, of which glycogen forms a normal constituent. It has been estimated that the percentage of glycogen in resting muscle varies from 0.5 to 0.9 per cent., and that in the musculature of the whole body there may be contained an amount of glycogen equal to that in the liver itself. Apparently muscular tissue, as well as liver-tissue, has a glycogenetic function—that is, it is capable of laying up a supply of glycogen from the sugar brought to it by the blood. The glycogenetic function of muscle has been demonstrated recently by Kulz,[1] who has shown that an isolated muscle irrigated with an artificial supply of blood to which dextrose had been added is capable of changing the dextrose to glycogen, as shown by the increase in the latter substance in the muscle after irrigation. Muscle glycogen is to be looked upon, probably, for reasons to be mentioned in the next paragraph, as a temporary and local reserve supply of material, so that, while we have in the liver a large general depot for the temporary storage of glycogen for the use of the body at large, the muscular tissue, which is the most active tissue of the body from a chemical standpoint, is also capable of laying up in the form of glycogen any excess of sugar brought to it. The fact that glycogen occurs so widely in the rapidly-growing tissues of embryos indicates that this glycogenetic function may at times be exercised by any tissue.

Conditions Affecting the Supply of Glycogen in Muscle and Liver.— In accordance with the view given above of the general value of glycogen— namely, that it is a temporary reserve supply of carbohydrate material which may be rapidly converted to sugar and oxidized with the liberation of energy— it is found that the supply of glycogen is greatly affected by conditions calling for increased oxidations in the body. Muscular exercise will quickly exhaust the supply of muscle and liver glycogen, provided it is not renewed by new food.

[1] *Zeitschrift für Biologie*, 1890, p. 237.

In a starving animal glycogen will finally disappear, except perhaps in traces, but this disappearance will occur much sooner if the animal is made to use its muscles at the same time. It has been shown also by Morat and Dufourt that if a muscle has been made to contract vigorously, it will take up much more sugar from an artificial supply of blood sent through it than a similar muscle which has been resting; on the other hand, it has been found that if the nerve of one leg is cut so as to paralyze the muscles of that side of the body, the amount of glycogen will increase rapidly in these muscles as compared with those of the other leg, that have been contracting meantime and using up their glycogen.

Formation of Urea in the Liver.—The nitrogen contained in the proteid material of our food is finally eliminated, after the metabolism of the proteid is completed, mainly in the form of urea. As will be explained in another part of this section, it has been definitively proved that the urea is not formed in the kidneys, the organs which eliminate it. It has long been considered a matter of the greatest importance to ascertain in what organ or tissues urea is formed. Investigations have now gone so far as to demonstrate that it arises chiefly in the liver, hence the property of forming urea must be added to the other important functions of the liver-cell. Schröder [1] performed a number of experiments in which the liver was taken from a freshly-killed dog and irrigated through its blood-vessels by a supply of blood obtained from another dog. If the supply of blood was taken from a fasting animal, then circulating it through the isolated liver was not accompanied by any increase in the amount of urea contained in it. If, on the contrary, the blood was obtained from a well-fed dog, the amount of urea contained in it was distinctly increased by passing it through the liver, thus indicating that the blood of an animal after digestion contains something which the liver can convert to urea. It is to be noted, moreover, that this power is not possessed by the organs generally, since blood from the well-fed animals showed no increase in urea after being circulated through an isolated kidney or muscle. As further proof of the urea-forming power of the liver Schröder found that if ammonium carbonate was added to the blood circulating through the liver—to that from the fasting as well as from the well-nourished animal—a very decided increase in the urea always followed. It follows from the last experiment that the liver-cells are able to convert carbonate of ammonia into urea. The reaction may be expressed by the equation $(NH_4)_2CO_3 - 2H_2O = CON_2H_4$. Schöndorff [2] in some recent work has shown that if the blood of a fasting dog is irrigated through the hind legs of a well-nourished animal, no increase in urea in the blood can be detected; but if the blood, after irrigation through the hind legs, is subsequently passed through the liver, a marked increase in urea results. Obviously, the blood in this experiment derives something from the tissues of the leg which the tissues themselves cannot convert to urea, but which the liver-cells can. Finally, in some remarkable experiments upon dogs made by four investigators (Hahn, Massen, Nencki, and Pawlow), which will be described

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[1] *Archiv für experimentelle Pathologie und Pharmakologie*, vols. xv. and xix., 1882 and 1885.

[2] *Pflüger's Archiv für die gesammte Physiologie*, 1893, vol. liv. p. 420.

briefly in the next section in connection with urea, it was shown that when the liver is practically destroyed there is a marked diminution in the urea of the urine, its place being taken by carbamic acid.   In birds uric acid takes the place of urea as the main nitrogenous excretion of the body, and Minkowski has shown that in them removal of the liver is followed by an important diminution in the amount of uric acid excreted.   From experiments such as these it is safe to conclude that urea is formed in the liver and is then given to the blood and excreted by the kidney.   When we come to describe the physiological history of urea (p. 274), an account will be given of the views held with regard to the antecedent substance or substances from which the liver produces urea.

Physiology of the Spleen.—Much has been said and written about the spleen, but we are yet in the dark as to the distinctive function or functions of this organ.   The few facts that are known may be stated briefly without going into the details of theories which have been offered at one time or another. The older experimenters demonstrated that this organ may be removed from the body without serious injury to the animal.   An increase in the size of the lymph-glands and of the bone-marrow has been stated to occur after extirpation ; but this is denied by others, and, whether true or not, it gives but little clue to the normal functions of the spleen.   Laudenbach[1] finds that one result of the removal of the spleen is a marked diminution in the number of red corpuscles and the quantity of hæmoglobin.   He infers, therefore, that the spleen is normally concerned in some way in the formation of red corpuscles. These facts are significant, but they need, perhaps, further confirmation.   The most definite facts known about the spleen are in connection with its movements.   It has been shown that there is a slow expansion and contraction of the organ synchronous with the digestion periods. After a meal the spleen begins to increase in size, reaching a maximum at about the fifth hour, and then slowly returns to its previous size.   This movement, the meaning of which is not known, is probably due to a slow vaso-dilatation, together, perhaps, with a relaxation of the tonic contraction of the musculature of the trabeculæ.   In addition to this slow movement, Roy[2] has shown that there is a rhythmic contraction and relaxation of the organ, occurring in cats and dogs at intervals of about one minute.   Roy supposes that these contractions are effected through the intrinsic musculature of the organ—that is, the plain muscle-tissue present in the capsule and trabeculæ—and he believes that the contractions serve to keep up a circulation through the spleen and to make its vascular supply more or less independent of variations in general arterial pressure.   These observations are valuable as indicating the importance of the spleen functions.   The fact that there is a special local arrangement for maintaining its circulation makes the spleen unique among the organs of the body, but no light is thrown upon the nature of the function fulfilled.   The spleen is supplied richly with nerve-fibres which when stimulated either directly or reflexly cause the organ to diminish in volume.   According to Schaefer,[3] these fibres are contained in

[1] *Centralblatt für Physiologie*, 1895, Bd. ix. S. 1.   [2] *Journal of Physiology*, 1881, vol. iii. p. 203.
[3] *Proceedings of the Royal Society*, London, 1896, vol. lix., No. 355.

the splanchnic nerves, which carry also inhibitory fibres whose stimulation produces a dilatation of the spleen.

The chemical composition of the spleen is complicated but suggestive. Its mineral constituents are characterized by a large percentage of iron, which seems to be present as an organic compound of some kind. Analysis shows also the presence of a number of fatty acids, fats, cholesterin, and, what is perhaps more noteworthy, a number of nitrogenous extractives such as xanthin, hypoxanthin, adenin, guanin, and uric acid. The presence of these bodies seems to indicate that active metabolic changes of some kind occur in the spleen. As to the theories of the splenic functions, the following may be mentioned: (1) The spleen has been supposed to give rise to new red corpuscles. This it undoubtedly does during fetal life and shortly after birth, and in some animals throughout life, but there is no reliable evidence that the function is retained in adult life in man or in most of the mammals. (2) It has been supposed to be an organ for the destruction of red corpuscles. This view is founded partly on very unsatisfactory microscopic evidence according to which certain large amœboid cells in the spleen ingest and destroy the old red corpuscles, and partly upon the fact that the spleen-tissue seems to be rich in an iron-containing compound. This theory cannot be considered at present as anything more than a suggestion. (3) It has been suggested that uric acid is produced in the spleen. This substance is found in the spleen, as stated above, and it has been shown recently by Horbacewsky that the spleen contains a substance from which uric acid or xanthin may readily be formed; but further investigation has shown that the same substance is found in lymphoid tissue generally. If, therefore, uric acid is produced in the spleen, it is a function of the large amount of lymphoid tissue contained in it, and a function which it shares with similar tissues in the rest of the body. The lymphoid tissue of the spleen must also possess the property of producing lymphocytes, since, according to the general view, these corpuscles are formed in lymphoid tissue generally wherever the so-called "germ-centres" occur. (4) Lastly, a theory has been supported by Schiff and Herzen, according to which the spleen produces something (an enzyme) which, when carried in the blood to the pancreas, acts upon the trypsinogen contained in this gland, converting it into trypsin. The experimental evidence upon which this view rests has not been confirmed by other observers.

G. The Kidney and the Skin as Excretory Organs.

The secretion of the kidneys is the *urine*. The means by which this secretion is produced, its relations to the histological structure of the kidney, and its connections with the blood- and nerve-supply of that organ will be found described in the section on Secretion. In this section will be discussed only the chemical composition of urine, and especially the physiological significance of its different constituents. The urine of man is a yellowish liquid varying greatly in depth of color. It has an average specific gravity of 1020, and an acid reaction. The acid reaction is not due to a free acid, but to an acid salt, the acid phosphate of sodium (NaH_2PO_4). Under certain normal conditions

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human urine may show a neutral or even a slightly alkaline reaction, especially after meals. In fact, the reaction of the urine seems to depend directly on the character of the food. Among carnivorous animals the urine is uniformly acid, and among herbivorous animals it is uniformly alkaline, so long as they are using a vegetable diet, but when starving or when living upon the mother's milk—that is, whenever they are existing upon a purely animal diet—the urine becomes acid. The explanation, as given by Drechsel, is that upon an animal diet more acids are produced (from the sulphur and phosphorus) than the bases present can neutralize, whereas upon a vegetable diet carbonates are formed from the oxidation of the organic acids of the food in quantities sufficient to neutralize the mineral acids. The chemical composition of urine is very complex. Among the constituents constantly present under the conditions of normal life we have, in addition to water and inorganic salts, the following substances: Urea; uric acid; xanthin; creatinin; hippuric acid; the urinary pigments (urobilin); sulphocyanides in traces; acetone; oxalic acid, probably as calcium oxalate; several ethereal sulphuric acids, such as phenol and cresol sulphuric acids, indoxyl sulphuric acid (indican), and skatoxyl sulphuric acid; aromatic oxy-acid; some combinations of glycuronic acid; some representatives of the fatty acids; and dissolved gases (N and CO_2). This list would be very much extended if it attempted to take in all those substances occasionally found in the urine. The complexity of the composition and the fact that so many different organic compounds occur or may occur in small quantities is readily understood when we consider the nature of the secretion. Through the kidneys there are eliminated not only what we might call the normal end-products of the metabolism of the tissues, excluding the CO_2, but also, in large part, the products of decomposition in the alimentary canal, the end-products of many organic substances occurring in our foods and not usually classed as food-stuffs, foreign substances introduced as drugs, etc., all of which are eliminated either in the form in which they are taken or as derivative products of some kind. We shall speak briefly of the most important of the normal constituents, dwelling especially upon their origin in the body and their physiological significance. For details of chemical properties, reactions, methods of preparation, etc. reference must be made to the Chemical section.

Urea.—Urea, which is given the formula CH_4N_2O, is usually considered as an amide of carbonic acid, having therefore the structural formula of $CO<^{NH_2}_{NH_2}$. It occurs in the urine in relatively large quantities (2 per cent. +). As the total quantity of urine secreted in twenty-four hours by an adult male may be placed at from 1500 to 1700 cubic centimeters, it follows that from 30 to 34 grams of urea are eliminated from the body during this period It is the most important of the nitrogenous excreta of the body, the end-product of the physiological oxidation of the proteids of the body, and also of the albuminoids when they appear in the food. If we know how much urea is secreted in a given period, we know approximately how much proteid has been broken down in the body in the same time. In round numbers, 1 gram

of proteid will yield $\frac{1}{3}$ gram of urea, as may be calculated easily from the amount of nitrogen contained in each. Since, however, some of the nitrogen of proteid is eliminated in other forms—uric acid, creatinin, etc.—even an exact determination of all the urea would not be sufficient to determine with accuracy the total amount of proteid broken down. This fact is arrived at more perfectly, as we shall explain later, by a determination of the total nitrogen of the urine and other excretions. In addition to the urine, urea is found in slight quantities in other secretions, in milk (in traces), and in sweat. In the latter liquid the quantity of urea in twenty-four hours may be quite appreciable—as much, for instance, as 0.8 gram—although such a large amount is found only after active exercise. It has been ascertained definitely that urea is not formed by the kidneys: it is brought to the kidneys in the blood for elimination, the cells of the convoluted tubules being especially adapted for taking up this material and transmitting it through their substance to the lumen of the tubules. That urea is not made in the kidneys is demonstrated by such facts as these: If blood, on the one hand, is irrigated through an isolated kidney, no urea is formed, even though substances (such as ammonium carbonate) from which urea is readily produced are added to the blood; on the other hand, urea is constantly present in the blood (0.0348 to 0.1529 per cent.), and if the two kidneys are removed, it continues to accumulate steadily in the blood as long as the animal survives. It has been ascertained that the urea is produced mainly in the liver; an account of some of the experiments demonstrating this fact is given on page 271. The most important questions that remain to be decided are, Through what steps is the proteid molecule metabolized to the form of urea? and, What is the antecedent substance brought to the liver, from which it makes urea? It is impossible to answer these questions perfectly, but recent investigations have thrown a great deal of light on the whole process, and they give hope that before long the entire history of the derivation of urea from proteids and albuminoids will be known. The results of this work may be stated briefly as follows:

1. Urea arises from proteids by a process of hydrolysis and oxidation, with the formation eventually of ammonia compounds, most probably the ammonium salt of carbamic acid, which are then conveyed to the liver and there changed to urea. The latter part of this theory—that the liver may produce urea from carbamate of ammonia—rests upon solid experimental evidence, as follows: In the first place, Drechsel found carbamic acid in the blood of dogs, and Drechsel and Abel have shown that it occurs normally in the urine of horses as calcium carbamate; and Abel has recently shown that it may be found in the urine of dogs or infants after the use of lime-water. Drechsel has shown, further, that ammonium carbamate may be converted into urea. If one compares the formulas of ammonium carbamate and urea, it is seen that the former may pass over into the latter by the loss of a molecule of water, as—

$$CO{<}^{NH_2}_{ONH_4} - H_2O = CO{<}^{NH_2}_{NH_2}.$$

Ammonium carbamate.   Urea.
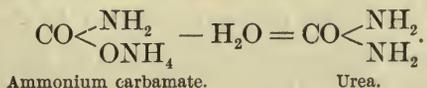
Drechsel supposes, however, that this dehydration is effected in an indirect manner; that there is first an oxidation removing two atoms of hydrogen, and then a reduction removing an atom of oxygen. He succeeded in showing that when an aqueous solution of ammonium carbamate is submitted to electrolysis, and the direction of the current is changed repeatedly so as to get alternately reduction and oxidation processes at each pole, some urea will be produced. These facts show the existence of ammonium carbamate in the body, and the possibility of its conversion to urea. Recent experiments made by Hahn, Pawlow, Massen, and Nencki[1] show that in dogs removal of the liver is followed by the appearance of carbamates in the urine and a marked decrease in the amount of urea. In these remarkable experiments a fistula was made between the portal vein and the inferior vena cava, the result of which was that the whole portal circulation of the liver was abolished, and the only blood that the organ received was through the hepatic artery. If, now, this artery was ligated or the liver was cut away, as was done in some of the experiments, then the result was practically an extirpation of the entire organ—an operation which has always been thought to be impossible with mammals. The animals in these investigations survived this operation for some time, but they died finally, showing a series of symptoms which indicated a deep disturbance of the nervous system. It was found that the symptoms of poisoning in these animals could be brought on before they developed spontaneously by feeding the dogs upon a rich meat diet, or with salts of ammonia or carbamic acid. Later investigations[2] showed that in normal animals the ammonia contents of the blood in the portal vein are from three to four times what is found in the arterial blood, but that after the operation described the ammonia in the arterial blood increases and at the time of the development of the fatal symptoms reaches about the percentage which is normal to the blood of the portal vein. It would seem from these investigations that the liver stands between the portal circulation and the general systemic circulation and protects the latter from the comparatively large amount of ammonia compounds contained in the portal blood by converting these compounds to urea. If the liver is thrown out of function, ammonia (ammonium carbamate) accumulates in the blood and causes death. The rich amount of ammonia in the portal blood seems to come chiefly from the decomposition of proteid material in the glands of the stomach and pancreas during secretion. Similar ammonia salts are probably formed in other active proteid tissues, since the percentage of ammonia in the tissues is considerably greater than in the blood, and these compounds also are doubtless converted to urea in the liver, in part at least. As to the origin of the ammonium carbamate there is little direct evidence. It comes in the long run, of course, from the nitrogenous food-stuffs, proteids and albuminoids. Drechsel's supposition is that the proteids first undergo hydrolytic cleavage, with the formation of amido- bodies such as leucin, tyrosin, aspartic acid, glycocoll, etc.; that these bodies undergo oxidation in the tissues, with the

[1] *Archiv für experimentelle Pathologie und Pharmakologie*, 1893, Bd. xxxii. S. 161.
[2] Nencki, Pawlow, and Zaleski: *Ibid.*, 1895, Bd. xxxvii. S. 26.

formation of NH_3, CO_2, and H_2O; and that the NH_3 and CO_2 then synthetically to form ammonium carbamate, which is carried to the liver and changed to urea. There is reason to believe that this formation of ammonium carbamate may take place in the tissues generally. The carbamate theory is at least in accord with the facts so far as known, and it is more complete and satisfactory than others which have been offered.

2. Even after the removal of the liver some urea is still found in the urine. This fact proves that other organs are capable of producing urea, but what the other organs are and by what process they make urea are points yet undetermined. It seems probable that some of the ammonia compounds which are now known to be formed in the tissues generally and to be given off to the blood may be converted into urea elsewhere than in the liver. Just as the glycogenic function of the liver-cells is shared to a less extent by other tissues—*e. g.* the muscle-fibres—it is possible that their power of converting ammonia salts to urea may be possessed to a lesser degree by other cells, and for this reason removal of the liver is not followed at once by a fatal result. Concerning this point, however, we must wait for further investigation. Drechsel has recently called attention to a method of obtaining urea directly from proteid outside of the body. His method is interesting not only because it is the first laboratory method discovered of producing urea from proteid, but also because it is possible that substantially the same process may occur inside the body. The method consists, in brief, in first boiling the proteid with an acid; HCl was used, together with some metallic zinc, so as to keep up a constant evolution of hydrogen and to exclude atmospheric oxygen. Among the products of decomposition of the proteid thus produced was a substance termed *lysatinin* ($C_6H_{11}N_3O$), and when this body was isolated and treated with boiling baryta-water ($Ba(OH)_2$) some urea was obtained. It is to be noted that in this case the urea was obtained not by the oxidation of the proteid, but by a series of decompositions or cleavages of the proteid molecule. Now, lysatinin occurs also in the body as one of the products of the continued action of trypsin on proteids (see p. 241). It is possible, therefore, that by further hydrolysis this substance, when it occurs, is converted to urea, and that normally a part of the urea arises from proteids by this process.

Uric Acid and Xanthin Bodies.—Uric acid, which has the formula $C_5H_4N_4O_3$, is found constantly, but in relatively small quantities, in human urine and in the urine of mammals generally. The total quantity in the urine of man under normal conditions varies from 0.2 to 1 gram every twenty-four hours. In the urine of birds and reptiles it forms the chief nitrogenous constituent. In these animals it takes the place physiologically of urea in mammalia in that it represents the main end-product of the metabolism of the proteids in the body. It is evident that at some point in the process the katabolism of the proteids in mammalia differs from that in birds and reptiles, since in the one urea, and in the other uric acid, is the outcome. Uric acid occurs in such small quantities in mammals that its place of origin has not been investigated successfully. It has been shown by Horbacewsky that in the lymphoid tissue generally, including

the adenoid tissue of the spleen, there is contained a substance which may be regarded as the mother-substance of uric acid. He ventures the hypothesis that uric acid represents an end-product in the metabolism of leucocytes, but the view at present can be regarded only as an interesting suggestion. Among birds and reptiles it has been shown that the liver is the chief producer of uric acid, just as it is of urea in mammals. Extirpation of the kidneys in birds leads to an accumulation of uric acid in the blood and tissues, showing that the kidneys do not produce the uric acid. Extirpation of the liver, on the contrary, leads to a marked diminution in the uric acid of the urine, and it is noteworthy that its place is taken by ammonium salts, probably ammonium lactate. This would indicate that in these animals proteid metabolism leads in some way to the formation of ammonium lactate, which is then carried to the liver and combined synthetically to make uric acid before being excreted by the kidneys. It is stated that in man also, in certain pathological conditions of the liver—for example, acute yellow atrophy and phosphorus-poisoning—lactates are found in the urine. Reasoning from analogy, we should suppose that in mammalia too uric acid is formed in the liver, but there is at present no positive evidence in favor of this view. Although the quantity of uric acid produced, or at least eliminated, during a day is so small in the mammalia, it is needless to say that the history of its formation, when completely known, will be of great importance, not only in that it will throw additional light upon the metabolism of the proteids in the body, and indeed upon the structure of the proteid molecule, but also because of its bearing upon the nature of certain pathological conditions; for it has been found that in fever, in leucæmia, and possibly in other diseases, there is an increased production of uric acid. Several other nitrogenous substances—xanthin, hypoxanthin, guanin, and adenin—forming members of what is known as the xanthin group, are closely related in composition to uric acid. Some or all of these substances may occur in the urine, especially xanthin and hypoxanthin, whose formulas are respectively $C_5H_4N_4O_2$ and $C_5H_4N_4O$. They are found only in minute quantities. To the extent that they occur they represent so much proteid broken down in the body; but what peculiarity in metabolism leads to their formation rather than to that of uric acid, or indeed urea, has not been discovered. They are found in greatest quantity in muscle, and are present, therefore, in meat extracts. It is interesting in this connection to call attention to the fact that theobromin (dimethyl-xanthin) and caffein (trimethyl-xanthin) are closely related to the xanthin bodies.

Creatinin.—Creatinin ($C_4H_7N_3O$) is a crystalline nitrogenous substance constantly found in urine. It is closely related to creatin ($C_4H_9N_3O_2$), the two substances differing by a molecule of water; the creatin changes to creatinin upon heating with mineral acids. Creatinin occurs in urine to the extent of about 1.12 grams per day in man. In dogs it has been found that the amount may vary between 0.5 and 4.9 grams per day according to the diet, an increase in the amount of meat in the diet causing an increase in the creatinin. This is readily explained by the fact that creatin is a constant constituent of muscle, and when taken into the stomach it is

eliminated in the urine as creatinin. It is evident, therefore, that part of the creatinin of the urine is derived from the meat eaten, and does not represent a metabolism within the body. A part, however, comes undoubtedly from the destruction of proteid within the body. In this connection the following facts are suggestive and worthy of consideration, although they cannot be explained satisfactorily: The mass of proteid tissue in the body is found in the muscles, and the end-product of the destructive metabolism of proteid is supposed to be chiefly urea. Nevertheless, urea is not found in the muscles, while creatin occurs in considerable quantities, as much as 90 grams being contained in the body-musculature at any one time. Only a small quantity (1.12 grams) of creatin is eliminated in the urine as creatinin during a day. What becomes of the relatively large quantity of creatin in the muscles? It has been suggested that it is one of the precursors of urea—that it represents an end-product of the proteid destroyed in muscle which is subsequently converted to urea in the liver or elsewhere. This supposition is supported by the fact that creatin may be decomposed readily in the laboratory, with the formation of urea among other products. But against this theory we have the important fact that creatin introduced into the blood is not converted to urea, but is eliminated as creatinin.

Hippuric Acid.—This substance has the formula $C_9H_9NO_3$. Its molecular structure is known, since upon decomposition it yields benzoic acid and glycocoll, and, moreover, it may be produced synthetically by the union of these two substances. Hippuric acid may be described, therefore, as a benzoyl-amido-acetic acid. It is found in considerable quantities in the urine of herbivorous animals (1.5 to 2.5 per cent.), and in much smaller amounts in the urine of man and of the carnivora. In human urine, on an average diet, about 0.7 gram is excreted in twenty-four hours. If, however, the diet is largely vegetable, this amount may be increased greatly. These last facts are readily explained. It has been found that if benzoic acid or related substances containing this group are fed to animals, they appear in the urine as hippuric acid. Evidently, a synthesis has taken place within the body, and Bunge and Schmiedeberg proved conclusively that in dogs, and probably, therefore, in man, the union of the benzoic acid to glycocoll occurs mainly in the kidney itself. We can understand, therefore, why vegetable foods which are known to contain substances belonging to the aromatic series and yielding benzoic acid should increase the output of hippuric acid in the urine. Since, however, in starving animals or in animals fed entirely on meat hippuric acid is still present, although reduced in amount, it follows that it arises in part as one of the results of body-metabolism. Among the various products of the breaking-down of the proteid molecule, it is probable that some benzoic acid occurs, and, if so, it is excreted in combination with glycocoll as hippuric acid. It should be added, finally, that some of the hippuric acid is supposed to be derived from the process of proteid putrefaction which occurs to a greater or less extent in the large intestine.

Conjugated Sulphates.—A good part of the sulphur eliminated in the

urine is in the form of ethereal salts with organic compounds of the aromatic and indigo series. Quite a number of these compounds have been described; the most important are the compounds with phenol ($C_6H_5OSO_2OH$), cresol ($C_7H_7O.SO_2OH$), indol ($C_3H_6NOSO_2OH$), and skatol ($C_9H_8NOSO_2OH$). These four substances, phenol, cresol, indol, and skatol, are formed in the intestine during the process of putrefactive decomposition of the proteids (p. 249). They are produced in small quantities, and they may be excreted in part in the feces, but in part they are absorbed into the blood. They are in themselves injurious substances, but in passing through the liver—which must of necessity happen before they get into the general circulation—they are synthetically combined with sulphuric acid, making the so-called "conjugated sulphates," which are harmless, and which are eventually excreted by the kidneys.

Water and Inorganic Salts.—*Water* is lost from the body through three main channels—namely, the lungs, the skin, and the kidney, the last of these being the most important. The quantity of water lost through the lungs probably varies within small limits only. The quantity lost through the sweat varies, of course, with the temperature, with exercise, etc., and it may be said that the amounts of water secreted through kidney and skin stand in something of an inverse proportion to each other; that is, the greater the quantity lost through the skin, the less will be secreted by the kidneys. Through these three organs, but mainly through the kidneys, the blood is being continually depleted of water, and the loss must be made up by the ingestion of new water. When water is swallowed in excess the superfluous amount is rapidly eliminated through the kidneys. The amount of water secreted may be increased by the action of diuretics, such as potassium nitrate and caffein, which probably act directly upon the secretory cells in the glomeruli.

The inorganic salts of urine consist chiefly of the chlorides, phosphates, and sulphates of the alkalies and the alkaline earths. It may be said in general that they arise partly from the salts ingested with the food, which salts are eliminated from the blood by the kidney in the water-secretion, and in part they are formed in the destructive metabolism which takes place in the body, particularly that involving the proteids and related bodies. Sodium chloride occurs in the largest quantities, averaging about 15 grams per day, of which the larger part, doubtless, is derived directly from the salt taken in the food. The phosphates occur in combination with Ca and Mg, but chiefly as the acid phosphates of Na or K. The acid reaction of the urine is caused by these latter substances. The phosphates come in part from the destruction of phosphorus-containing tissues in the body, but chiefly from the phosphates of the food. The sulphates of urine are found partly conjugated with organic substances, as described above, and partly as simple sulphates. The total quantity of sulphuric acid eliminated is estimated to average about 2.5 grams per day. Sulphur constitutes a constant element of the proteid molecule, and the quantity of it eliminated in the urine may be used, as in the case of nitrogen, to determine the total destruction of proteid within a given period.

Functions of the Skin.—The physiological activities of the skin are varied. It forms, in the first place, a sensory surface covering the body, and interposed, as it were, between the external world and the inner mechanism. Nerve-fibres of pressure, temperature, and pain are distributed over its surface, and by means of these fibres reflexes of various kinds are effected which keep the body adapted to changes in its environment. The physiology of the skin from this standpoint is discussed in the section on Cutaneous Sensations. Again, the skin plays a part of immense value to the body in regulating the body-temperature. This regulation, which is effected by variations in the blood-supply or the sweat-secretion, is described at appropriate places in the sections on Animal Heat, Circulation, and Secretion. In the female, during the period of lactation, the mammary glands, which must be reckoned among the organs of the skin, form an important secretion, the milk; the physiology of this gland is described in the sections on Secretion and Reproduction. In this section we are concerned with the physiology of the skin from a different standpoint—namely, as an excretory organ. The excretions of the skin are formed in the sweat-glands and the sebaceous glands. The sweat-glands are distributed more or less thickly over the entire surface of the body, with the exception of the prepuce and glans penis, while the sebaceous glands, usually in connection with the hairs, are also found everywhere except upon the palms of the hands and the soles of the feet.

Sweat.—Sweat, or perspiration, which is the secretion of the sweat-glands, is a colorless liquid with a peculiar odor and a salty taste. Its specific gravity is given at 1004, and in man it usually has an acid reaction. As can readily be understood, the quantity secreted in twenty-four hours varies greatly, the secretion being influenced by variations in temperature, by exercise, and by psychical and pathological conditions; an average estimate places the daily secretion at from 700 to 900 grams. Chemically, the secretion consists of water and inorganic salts, traces of fats, fatty acid, cholesterin, and urea. Of the inorganic salts, $NaCl$ is by far the most abundant: it occurs in quantities varying from 2 to 3.5 parts per thousand. The elements of the sweat which are of importance from an excretory standpoint are water, inorganic salts, and urea or related nitrogenous compounds. As was said above, sweat constitutes the second in importance of the three main channels through which water is lost from the body. The quantity eliminated in the sweat is to a certain extent inversely proportional to that secreted by the kidneys; but the physiological value of the secretion of water by the sweat-glands seems to lie not so much in the fact that it is necessary in maintaining the water-equilibrium of the blood and tissues as in the important part it takes in controlling the heat-loss from the skin: the greater the evaporation of sweat, the greater the loss of heat. The urea is described as occurring in traces. As far as it occurs, it represents, of course, so much proteid destroyed, but usually in calculating the proteid loss of the body this element has been neglected. Argutinsky demonstrated, however, that in special cases—namely, during periods of unusual muscular work or after vapor-baths—the total weight of nitrogen eliminated by the skin may be of consider-

able importance, amounting to as much as 0.7 to 0.8 gram. Under ordinary circumstances the excretion of urea and related compounds through the skin must be regarded as of very subsidiary importance, but the amount may be increased markedly under pathological conditions.

Sebaceous Secretion.—The sebaceous secretion is an oily, semi-liquid material, the quantity of which cannot be estimated even approximately. Chemically, it consists of water and salts, albumin and epithelium, fats and fatty acids. Its excretory importance in connection with the metabolism of the body must be slight. Its chief physiological value must be sought in its effect upon the hairs, which are kept oiled and pliant by the secretion. Moreover, it forms a thin, oily layer over most of the surface of the skin; and we may suppose that this layer of oil is of value in two ways—in preventing too great a loss of water through the skin, and in offering an obstacle to the absorption of aqueous solutions brought into contact with the skin.

Excretion of CO_2.—In some of the lower animals—the frog, for example—the skin takes an important part in the respiratory exchanges, eliminating CO_2 and absorbing O. In man, and presumably in the mammalia generally, it has been ascertained that changes of this kind are very slight. Estimates of the amount of CO_2 given off from the skin of man during twenty-four hours vary greatly, but the amount is small, and is certainly less than one one-hundredth part of the amount given off through the lungs.

H. Body-metabolism; Nutritive Value of the Food-stuffs.

Determination of Total Metabolism.—We have so far studied the changes that the food-stuffs undergo during digestion, the form in which they are absorbed into the blood, their history in the tissues to some extent, and the final condition in which, after being decomposed in the body, they are eliminated in the excreta. To ascertain the true nutritional value of the food-stuffs it is of the utmost importance that we should have some means of estimating accurately the kind and the amount of body-metabolism during a given period in relation to the character of the diet used. Fortunately, this end may be reached by a careful study of the excreta. The methods employed can readily be understood in principle from a brief description. It has been made sufficiently clear before this, perhaps, that by determining the total amount of the nitrogenous excreta we can reckon back to the amount of proteid (or albuminoid) destroyed in the body. In the case of proteids or albuminoids which undergo physiological oxidation all the nitrogen appears in the forms of urea, uric acid, creatinin, xanthin, etc., which are eliminated mainly through the urine, and may therefore be collected and determined. The following practical facts are, however, to be borne in mind in this connection: The nitrogenous excretion of the urine is mainly in the form of urea which can be estimated as such, but it is much more accurate to determine the total nitrogen in the urine during a given period, using some one of the approved methods for nitrogen-determination, and to calculate back from the amount of nitrogen to the amount of

proteid. By this means all the nitrogenous excreta which may occur in the urine are allowed for; and since the various proteids differ but little in the amount of nitrogen which they contain, the average being from 15.5 to 16 per cent., it is only necessary to multiply the total quantity of nitrogen found in the excretions by 6.25 (proteid molecule : N :: 100 : 16) to ascertain the amount of proteid destroyed. In accurate calculations it is necessary to determine the total nitrogen in the feces as well as in the urine, and for two reasons: first, in ordinary diets a certain proportion of vegetable and animal proteid escapes digestion, and this amount must be determined and deducted from the total proteid eaten in order to ascertain what nitrogenous material has actually been taken into the body; second, the secretions of the alimentary canal contain a certain quantity of nitrogenous material, which represents a genuine excretion, and should be included in estimates of the total proteid-destruction. Practical experience has shown that in man about 29 per cent. of the total nitrogen of the feces has this latter origin. The nitrogen eliminated as urea, etc. in the sweat, milk, and saliva is neglected under ordinary circumstances because the amount is too small to affect materially any calculations made. To determine the total amount of non-nitrogenous material destroyed in the body during a given period, two data are required: first, the total nitrogen in the excreta of the body; second, the total amount of carbon given off from the lungs and in the various excreta. From the total nitrogen one calculates how much proteid was destroyed, and, deducting from the total carbon the amount corresponding to this quantity of proteid, what remains represents the carbon derived from the metabolism of the non-nitrogenous material—that is, from the fat or carbohydrate. By methods of this kind it is possible to reckon back from the excreta to the total amount of material, consisting of proteid, fat, and carbohydrate, which has been consumed in the body within a certain period. If, now, by analyzing the food or by making use of analyses already made (see p. 216), one determines how great a quantity of proteid, fat, and carbohydrate has been taken into the body in the same period, then, by comparison of the total ingesta and egesta, it is possible to strike a balance and to determine whether all the proteid, fat, and carbohydrate of the food have been destroyed, or whether some of the food has been stored in the body, and in this case whether it is nitrogenous or non-nitrogenous material, or, lastly, whether some of the reserve material of the body, nitrogenous or non-nitrogenous, has been destroyed in addition to the supply of food. It is needless to remark that "balance experiments" of this character are very laborious, particularly as they must be made over long intervals—one or more days. Nevertheless, a great deal of work of this kind has been done upon man as well as upon lower animals, especially by Voit[1] and Pettenkofer. In the experiments upon man the urine and feces were collected carefully and the total nitrogen was determined; at the same time the total quantity of CO_2 given off from the lungs was estimated for the entire period. The determination of the CO_2 was made possible by keeping the man in a specially-constructed chamber through which air was drawn by means of a

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[1] *Hermann's Handbuch der Physiologie,* 1881, vol. vi.

pump; the total quantity of air drawn through was indicated by a gasometer, and a measured portion of this air was drawn off through a separate gasometer and was analyzed for its CO_2. It was found that the method is practicable: that by the means described a nearly perfect balance may be struck between the income and the outgo of the body. Experiments of this general character have been used to determine the fate of the food-stuffs in the body under different conditions, the essential part that each food-stuff takes in general nutrition, and so on. In this and the succeeding sections we shall have to consider some of the main results obtained; but first it will be convenient to define two terms frequently used in this connection—namely, "nitrogen equilibrium" and "carbon equilibrium."

Nitrogen Equilibrium.—By "nitrogen equilibrium" we mean that condition of an animal in which, within a definite period, the nitrogen of the excreta is equal in amount to the nitrogen of the food; in other words, that condition in which the proteid (and albuminoid) food eaten exactly covers the loss of proteid (and albuminoid) in the body during the same time. If an animal is giving off more nitrogen in its excreta than it receives in its food, then the animal must be losing proteid from its body; if, on the contrary, the food that it eats contains more nitrogen than is found in the excreta, the animal must be storing proteid in its body. The condition of nitrogen equilibrium is the normal state of a properly-nourished adult. It is important to remember that nitrogen equilibrium may be maintained at different levels; that is, one may begin with a starving animal and slowly increase the amount of nitrogenous food until nitrogen equilibrium is just established. If now the amount of nitrogenous food is increased—say doubled—the excess does not, of course, continue to be stored up in the animal's body; on the contrary, in a short time the amount of proteid destroyed in the body will be increased to such an extent that nitrogen equilibrium will again be established at a higher level, the animal in this case eating more and destroying more. The highest limit at which nitrogen equilibrium can be maintained is determined, apparently, by the power of the stomach and the intestines to digest and absorb proteid food. Further details upon this point will be given presently, in describing the nutritive value of the food-stuffs.

Carbon Equilibrium.—The term "carbon equilibrium" is sometimes used to describe the condition in which the total carbon of the excreta (occurring in the CO_2, urea, etc.) is exactly covered by the carbon of the food. As one can readily understand, an animal might be in a condition of nitrogen equilibrium and yet be losing or be gaining in weight, since, although the consumption of proteids in the body might just be covered by the proteids of the food, the consumption of non-proteids, fats and glycogen, might be greater or less than was covered by the supply of food. In addition, we might speak of an equilibrium as regards the water, salts, etc., although these terms are not generally used. An adult in good health usually so lives as to keep in both nitrogen and general body equilibrium—that is, to maintain his normal weight—while slight variations in weight from time to time are probably for the most part

due to a loss or a gain in body-fat—in other words, to changes in the carbon equilibrium.

Nutritive Importance of the Proteids.—The digestion and absorption of proteids have been considered in previous sections. We believe that the digested proteid is absorbed into the blood in a slightly modified form, with the exception of the variable quantity which suffers decomposition into the simpler amido- compounds while in the intestine as a result of putrefaction or of the prolonged action of trypsin. Subsequently this proteid material passes into the lymph and is brought into contact with the tissues. Its main nutritive importance lies in its relations to the tissues, and, speaking generally, we may say that the final fate of the proteid molecule is that it undergoes a physiological oxidation whereby the complex molecule is broken down to form the simpler and more stable compounds CO_2, H_2O, and urea. This destruction of the proteid molecule takes place in or under the influence of the living cells, and it gives rise to a liberation of energy mainly in the form of heat. It is impossible to follow the various ways in which this physiological oxidation takes place. It is probable, however, that some of the proteid undergoes destruction without ever becoming a part, an organized part, of the living cells, although its oxidation is effected through the agency of the cells. It has been proposed by Voit[1] to designate the proteid which is oxidized in this way as "the circulating albumin or proteid." According to Voit, a well-fed animal has in its lymph and tissues always a certain excess of proteid which is to undergo the fate of the circulating proteid, and this supposition is used to explain the fact that for the first day or so a starving animal metabolizes more proteid, as determined by the nitrogenous excreta, than in the subsequent days, after the supply of the circulating proteid has been destroyed. A portion of the proteid food, however, before its final destruction is utilized to replace the nitrogenous waste of the tissues; it is built up into living protoplasm to supply the place of organized tissue which has undergone disassimilation or to furnish new tissue in growing animals. To the proteid which is built up into tissue Voit gives the name of "organeiweiss," the best translation of which, perhaps, is "tissue-proteid." It should be stated that this division of the proteid into circulating proteid and tissue-proteid has been severely criticised by some physiologists, but it has the merit at least of furnishing a simple explanation of some curious facts with regard to the use of proteid in the body. To avoid misunderstanding, it is well to say that the separation into circulating proteids and tissue-proteids does not mean that the proteid which is absorbed from the alimentary canal is of two varieties. The terms refer to the final fate of the proteid in the body: a certain portion is utilized to replace protoplasmic tissue, and it then becomes "tissue-proteid," while the balance is metabolized in various ways and constitutes the "circulating proteid." Any given molecule of proteid, as far as is known, may fulfil either function. With regard to the general nutritive value of proteids, it has been demonstrated clearly that they are abso-

[1] *Hermann's Handbuch der Physiologie*, 1881, vol. vi. p. 300.

lutely necessary for the formation of protoplasmic tissue. An animal fed only on non-nitrogenous food such as fats and carbohydrates will inevitably starve to death in time: this has been shown by actual experiments, and, besides, it follows from *a priori* considerations. Protoplasm contains nitrogen; fats and carbohydrates are non-nitrogenous, and therefore cannot be used to make new protoplasmic material. It is requisite, moreover, not only that the food shall contain some nitrogen, but that this nitrogen shall be in the form of proteid. If an animal is fed upon a diet containing fats and carbohydrates and nitrogenous material other than proteids, such as amido-acids or gelatin, nitrogenous equilibrium cannot be maintained. There will be a steady loss of nitrogen in the excreta, due to a breaking-down of proteid tissue within the body, and the final result of maintaining such a diet would be the death of the animal. It may be said, then, with certainty of animal metabolism that proteid food is absolutely necessary for the formation of new protoplasm; its place in this respect cannot be taken by any other element of our food. But, in addition to this use, proteid, as has been described above, may be oxidized in the body without being first constructed into protoplasmic material. According to an older theory in physiology, advanced by Liebig, food-stuffs were either plastic or respiratory; by plastic foods he meant those which were built into tissue, and he supposed that the proteids belonged to this class; by respiratory foods he meant those which were oxidized or burnt in the body to produce heat: the fats and carbohydrates constituted this class. We now know that proteids are respiratory as well as plastic in the terms of this theory; they serve as sources of energy as well as to replace tissue, and Liebig's classification has therefore fallen into disuse. Our present ideas of the twofold use of proteid food may be supported by many observations and experiments, but perhaps the most striking proof of the correctness of these views is found in the fact that a carnivorous animal can be kept in both nitrogen and carbon equilibrium upon a meat diet only, excluding for the time a consideration of the water and inorganic salts. Pettenkofer and Voit kept a dog weighing 30 kilograms in nitrogen and carbon equilibrium upon a diet of 1500 grams of lean meat per day, and by increasing the diet to 2500 grams per day the animal even gained in weight, owing to an increase in fat. Pflüger states also that he was able to keep a dog in body-equilibrium as long as eight months upon a meat diet. Facts like these demonstrate that the animal organism may get all its necessary energy from proteid food alone, although, as we shall see later, it is more economical and more beneficial to get a part of it at least from the oxidation of fats and carbohydrates. Adopting the theory of "circulating proteids," we may say that any excess of proteid above that utilized for tissue-repair or tissue-growth will be metabolized in the body, with the liberation of energy. It makes no difference how much proteid material we consume: the excess beyond that used to replace tissue is quickly destroyed in some way, and its nitrogen appears in the urine as urea or one of the related compounds. A good example of the power of the tissues to oxidize large amounts of proteid is given in the following experiment, selected from a

paper by Pflüger. Dog, weight 28.1 kilograms, fed at 11 A. M. with 2070.7 grams of meat:

2070.7 grams of meat contain . . . . 69.2 grams N.
Total nitrogen eliminated in urine and feces in twenty-four
    hours (7 A. M. to 7 A. M.) . . . . 71.2 " "
             Deficit of N . . . . 0.96 grams.

The total nitrogen in the urine alone was 68.5 grams.

In urine from 7 A. M. to 11 A. M., the fasting period . . . . . 6.9 grams.
In urine from 11 A. M. to 7 A. M., time after feeding . . . . . 61.6 "

Therefore in the four hours of fasting the animal eliminated in his urine 1.7 grams N per hour, while in the twenty hours after eating he excreted 3.1 grams N per hour. This experiment shows not only the completeness with which an excessive proteid diet is handled by the tissues, but also the rapidity with which the excess is destroyed. In so far as proteid food is burnt in the body only as a source of energy and without being used to form new tissue, its place can be supplied in part, but only in part, by non-nitrogenous foodstuffs—carbohydrates and fats. The double use of proteid as a tissue-former and an energy-producer would seem to imply that if, in any given case, sufficient proteid were used in the diet to cover the tissue-waste, the balance of the diet might be composed of fats and carbohydrates, and the animal thereby be kept in nitrogenous equilibrium. Apparently this is not the case, as is seen from experiments of the following character: When an animal is allowed to starve, the nitrogen in the urine, after the first few days, becomes practically constant, and represents the amount of oxidation of proteid tissue taking place in the body. If, now, the animal is given an amount of proteid just equal to that being destroyed in the body, nitrogenous equilibrium is not established; some of the body-proteid continues to be lost, and to get the animal into equilibrium a comparatively large excess of proteid must be given in the food. The same result holds if carbohydrates and fats are given along with the proteid, with the exception that upon this diet nitrogen equilibrium is more readily established—that is, less proteid is required in the food. Upon the theory of circulating proteids and tissue-proteids, this fact may be accounted for by saying that of the proteid given as food, a part always undergoes destruction as circulating proteid without going to form tissue, so that to cover tissue-waste a larger amount of proteid must be taken as food than would be necessary if it could all be used exclusively for the repair of tissue. Carbohydrates and fats diminish the amount of proteid destroyed as circulating proteid, and thereby enable us to keep in nitrogen equilibrium on a smaller proteid diet. With albuminoid food (gelatin) the facts seem to be different. If albuminoids be given in the food together with proteids or with proteids and a non-nitrogenous food-stuff (fats or carbohydrates), nitrogen equilibrium may be established upon a much smaller amount of proteid than in the case of a diet consisting of proteid alone or of proteid together with fats and carbohydrates. It seems probable that albuminoids can take the place entirely of circulating proteids, so that only enough

proteid need be given to cover actual tissue-waste. This point will be referred to again in speaking of the value of the albuminoids.

Luxus Consumption.—The fact that normally more proteid is eaten, even in a mixed diet, than is necessary to cover the actual tissue-waste led some of the older physiologists to speak of the excess as unnecessary, a luxus, and the rapid destruction of the excess in the body was described as a "luxus consumption." There can be no doubt about the fact that proteid may be, and normally is, eaten in excess of what is necessary to repair tissue-waste, or in excess of what is requisite to maintain nitrogenous equilibrium at a low level. But it is altogether improbable that the excess is really a "luxus." It has been stated, in speaking of nitrogenous equilibrium, that an animal may be kept in this condition upon a certain minimal amount of proteid, or upon various larger amounts up to the limit of the power of the alimentary canal to digest and absorb; but it has also been shown (Munk[1]) that if an animal is fed upon a diet containing quantities of proteid barely sufficient to maintain N equilibrium, it will after a time show signs of malnutrition. It seems to be necessary, as Pflüger pointed out, that the tissues should have a certain excess of proteid to destroy in order that their nutritional or metabolic powers may be kept in a condition of normal activity. Hence we find that well-nourished individuals habitually consume more proteid than would theoretically suffice for N equilibrium. For example, the average diet of an adult contains, or should contain, from 100 to 118 grams of proteid per day, but it has been shown that nitrogen and body equilibrium in man may be maintained, for short periods at least, upon 40 grams of proteid a day, provided large amounts of fats or carbohydrates are eaten. It is scarcely necessary to add that this beneficial excess has a limit, and that too great an excess of proteid food may cause troubles of digestion as well as of general nutrition.

Nutritive Value of Albuminoids.—The albuminoid most frequently occurring in food is gelatin. It is derived from *collagen* of the connective tissues. Collagen of bones or of connective tissue takes up water when boiled and becomes converted into gelatin. We eat gelatin, therefore, in boiled meats, soups, etc., and, besides, it is frequently employed directly as a food in the form of table-gelatin. Collagen has the following percentage composition: C, 50.75 per cent.; H, 6.47; N, 17.86; O, 24.32; S, 0.6. It resembles the proteid molecule closely in chemical composition, and it would seem that the tissues might use it as they do proteid, for the formation of new protoplasm. Experiments, however, have demonstrated clearly that this is not the case. Animals fed upon albuminoids together with fats and carbohydrates do not maintain N equilibrium; a certain proportion of tissue breaks down, giving an excess of nitrogen in the urine. The final result of such a diet would be continued loss of weight and, finally, malnutrition and death. Gelatin, however, is readily digested, gelatoses and gelatin peptones being formed; these are absorbed and oxidized in the body, with the formation of CO_2, H_2O, and urea or some related nitrogenous product. Gelatin serves, then, as a source

[1] DuBois-Reymond's *Archiv für Physiologie*, 1891, p. 338.

of energy to the body in the same sense as do carbohydrates and fats. When any one of these three substances is used in a diet, the proportion of proteid necessary for the maintenance of N equilibrium may be reduced greatly. Upon the theory of circulating proteids, this is explained by saying that these substances are burnt in place of proteid, and that the proportion of this latter material which undergoes the fate of circulating proteid is thereby diminished. Actual experiments have shown that gelatin is more efficacious than either fats or carbohydrates in protecting the proteid in the body, and it has been suggested, therefore, that it may take the place, partly or completely, of the circulating proteid, according to the amount fed. If this suggestion is true, we may say that gelatin has a nutritive value the same as that of the proteids, except that it cannot be constructed into living proteid. The relative value of fats, carbohydrates, and gelatin in protecting proteid from destruction in the body is illustrated by the following experiment, reported by Voit. A dog weighing 32 kilograms was fed alternately upon proteid and sugar, proteid and fat, and proteid and gelatin :

| | Nourishment (grams). | | | Calculated destruction of flesh |
Meat.	Gelatin.	Fat.	Sugar.	in body (grams).
400	—	200	—	450
400	—	—	250	439
400	200	—	—	356

Munk [1] has attempted recently to determine how far the proteids of food may be replaced by gelatin. In these experiments a dog was brought into a condition of nitrogenous equilibrium upon a diet of flesh-meal, rice, and lard, containing 9.73 grams of nitrogen. During the period this diet was continued the animal, whose weight was 16.5 kilograms, was oxidizing in its body 3.7 grams of proteid daily for each kilogram of weight. In a second period lasting four days the quantities of rice and lard were the same as before, but the proteid in its diet was reduced to 8.2 grams, which contained 1 gram of nitrogen ; the balance of the nitrogen was supplied in the form of gelatin, so that in round numbers only one-sixth of the required daily amount of nitrogen was given as proteid. The result was that the animal maintained its nitrogen equilibrium for the short period stated. It was found that the experiments could not be continued longer than four days, owing to the growing dislike of the animal for the gelatin food. During the second period the animal was receiving in its food and burning in its body only 0.5 gram of proteid daily for each kilogram of weight, as against 3.7 grams upon a normal diet. It would not be possible to substitute fats or carbohydrates for the proteids of the daily diet to anything like the same extent without causing a consumption of some of the store of proteid material within the body.

Nutritive Value of Fats.—The fats of food are absorbed into the lacteals as neutral fats. They eventually reach the blood in this condition, and are afterward in some way consumed by the tissues. The final products of their oxidation must be the same as when burnt outside the body—namely, CO_2

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[1] *Pflüger's Archiv für die gesammte Physiologie*, 1894, vol. lviii. p. 309.

and H_2O—and a corresponding amount of energy must be liberated.   Speaking generally, then, the essential nutritive value of the fats is that they furnish energy to the body, and, from a chemical standpoint, they must contain more available energy, weight for weight, than the proteids or the carbohydrates (see p. 303).   In a well-nourished animal a large amount of fat is found normally in the adipose tissues, particularly in the so-called "panniculus adiposus" beneath the skin.   Physiologically, this body-fat is to be regarded as a reserve supply of nourishment.   When food is eaten and absorbed in excess of the actual metabolic power of the body, the excess is stored in the adipose tissue as fat, to be drawn upon in case of need—as, for instance, during partial or complete starvation.   A starving animal, after its small supply of glycogen is exhausted, lives entirely upon body-proteids and fats ; the larger the supply of fat, the more effectively will the proteid tissues be protected from destruction.   In accordance with this fact, it has been shown that when subjected to complete starvation a fat animal will survive longer than a lean one.   Our supply of fat is called upon not only during complete abstention from food, but also whenever the diet is insufficient to cover the oxidations of the body, as in deficient food, sickness, etc.

Formation of Fat in the Body.—The origin of body-fat has always been an interesting problem to physiologists.   Naturally, the first supposition made was that it comes directly from the fat of the food.   According to this view, a certain proportion of the fat of the food was supposed to be deposited directly in the cells of adipose tissue, and in this way all our supply of fat originated. This theory was soon disproved.   It was shown, especially upon cows and pigs, that the amount of fat formed in the body within a given time, including the fat of milk in the case of the cow, might be far in excess of the total amount of fat taken in the food during the same period, thus demonstrating that a certain proportion at least of the body-fat must have some other origin.   Moreover, the genesis of the fat-droplets in fat-cells, as studied under the microscope, did not agree with the old view ; and there was the further fact that each animal has its own peculiar kind of fat; as Liebig says, " In hay or the other fodder of oxen no beef-suet exists, and no hog's lard can be found in the potato refuse given to swine."   In fact, the evidence was so conclusive against this theory that physiologists for a time were led to adopt the opposite view that no fat at all can be obtained directly from the fat of the food.   However, it has now been shown that under certain conditions fat may be deposited directly in the tissues from the fat of food.   Lebedeff, and afterward Munk, proved that if a dog is first starved until the reserve supply of fat in the body is practically used up, and it is then fed richly upon foreign fats, such as rape-seed oil, linseed oil, or mutton tallow, it will again lay on fat, and some of the foreign fat may be detected in its body.   The conditions necessary to be fulfilled in order to get this result make it probable that under normal conditions none of the fat of the body is derived directly from the fat of the food.   On the contrary, the fat of the food is completely oxidized, and our body-fat is normally constructed anew from either proteids or carbohydrates.   As to its origin from

proteid, Voit has devoted numerous researches to the purpose of demonstrating that this is the main source of body-fat. His belief is that in the course of metabolism the proteid molecule undergoes a cleavage, with the formation of a nitrogenous and a non-nitrogenous part. The former, after further changes, is eliminated in the form of urea, etc.; the latter may be converted into fat, or possibly into glycogen. The theoretical maximum of fat which can arise in this way is 51.5 per cent. of the entire amount of proteid. Voit attempted to demonstrate this theory by actual experiments. He showed that dogs fed upon large amounts of lean meat did not give off as much carbon in the excreta as they received in the food. The excess of carbon must have been retained in the body, and, in all probability, in the form of fat. As corroborative evidence he cites the apparently direct conversion of proteid material into fat in such cases as the formation of fat-droplets in the fat-cells or cells of the mammary glands, and in muscle-fibres and liver-cells undergoing fatty degeneration; but evidence of this latter character is not conclusive, since we have no immediate proof that the fat arises directly from the proteid material in the cells. Voit's experimental evidence has been questioned recently by Pflüger, his criticisms being directed mainly toward the calculations involved in Voit's experiments. The result of this criticism has been to make us more cautious in attributing the origin of body-fat solely or mainly to proteids, but as regards the possibility of some proteid being converted into fat in the body there can be no reasonable doubt. It has been proved (p. 268) that glycogen may be formed from proteid, and since it is now generally accepted that fats are formed from carbohydrates, the possibility of an indirect production of fats from proteids seems to follow necessarily.

The connection between the carbohydrates of the food and the fat of the body has been a subject of discussion and investigation among physiologists for a number of years. It was the original belief of Liebig that carbohydrates are the source of body-fat. This view was afterward abandoned under the influence of the work of Pettenkofer and Voit, but renewed investigations seem to have re-established it upon solid experimental grounds. In some older experiments of Lawes and Gilbert it was shown that the fat laid on by a young pig during a certain period was greater than could be accounted for by the total fat in the food during that period, plus the theoretical maximum obtainable from the proteid fed during the same time. Of more recent experiments demonstrating the same point, a single example may be quoted from Rubner,[1] as follows: A small dog, weighing 6.2 kilograms, was fed richly with meat for two days and was then starved for two days; its weight at the end of this time was 5.89 kilograms. The animal was then given for two days a diet of cane-sugar 100 grams, starch 85 grams, and fat 4.7 grams. It was kept in a respiration apparatus and its total excretion of nitrogen and carbon was determined:

Total C excretion . . . . 87.10 grams C.
" C ingesta . . . . 176.6 " "
89.5 " " retained in the body.

[1] *Zeitschrift für Biologie*, 1886, vol. 22, p. 272.

The total nitrogen excreted $= 2.55$ grams. The carbon contained in the proteid thus broken down plus that in the 4.7 grams of fat $= 13$ grams. If we make the assumption that all of the C from these two sources was retained within the body, there would still be a balance of 76.5 grams C ($89.5 - 13.0$) which must have been stored in the body either as glycogen or as fat. The greatest possible storage of glycogen was estimated at 78 grams $= 34.6$ grams C, so that $76.5 - 34.6 = 41.9$ grams C as the minimal amount which must have been retained as fat and must have arisen from the carbohydrates of the food. Similar experiments have been made upon herbivorous animals, and as the result of investigations of this character we are compelled to admit that the carbohydrates form one source, and possibly the main source, from which the body-fats are derived. This belief accords with the well-known fact that in fattening stock the best diet is one containing a large amount of carbohydrate together with a certain quantity of proteid. On the view that fats were formed only from proteids, the efficacy of the carbohydrates in such a diet was supposed to lie in the fact that they protected a part of the proteid from oxidation, and thus permitted the formation of fat from proteid; but it is now believed that the carbohydrates of a fattening diet are, in part, converted directly to fat, although the chemistry of the transformation is not as yet understood. Diets, such as the well-known Banting diet, intended to reduce obesity are characterized, on the contrary, by a small proportion of carbohydrates and a relative excess of proteid.

Nutritive Value of Carbohydrates.—The nutritive importance of the carbohydrates is similar in general to that of the fats; they are oxidized and furnish energy to the body. In addition, as has been described in the preceding paragraph, they may be converted into fat and stored in the body as a reserve supply of nourishment. As a matter of fact, the carbohydrates form the bulk of ordinary diets. They are easily digested, easily oxidized in the body, and from a financial standpoint they form the cheapest food-stuff. The final products in the physiological oxidation of carbohydrates must be CO_2 and H_2O. Inasmuch as the H and O in the molecule already exist in the proper proportions to form H_2O ($C_6H_{12}O_6$, $C_{12}H_{22}O_{11}$), it follows that relatively less oxygen will be needed in the combustion of carbohydrates than in the case of proteids or of fats. Whatever may be the actual process of oxidation, we may consider that only as much O is needed as will suffice to oxidize the C of the sugar to CO_2.

Hence the ratio of O absorbed to CO_2 eliminated, $\dfrac{CO_2}{O_2}$, a ratio which is known

as the respiratory quotient, will approach nearer to unity as the quantity of carbohydrates in the diet is increased. From our study of the digestion of carbohydrates (p. 257) we have found that most of the carbohydrates of our food pass into the blood as dextrose (or levulose), and any excess above a certain percentage is converted temporarily to glycogen in the liver, the muscles, etc., to be again changed to dextrose before being used. The sugar undergoes final oxidation in the tissues to CO_2 and H_2O. While it is possible that this oxidation may be direct—that is, that the sugar may be burnt directly to CO_2 and

H_2O—it is usually supposed to be preceded by a splitting of the sugar molecule. The steps in the process are not definitely known; according to one hypothesis, the molecule first undergoes cleavage, with the formation of lactic acid $(C_6H_{12}O_6 = 2C_3H_6O_3)$, which is then oxidized. According to another hypothesis, the sugar first breaks down, with the formation of alcohol and CO_2, as in the yeast fermentation outside the body.

There have been discovered recently in connection with the pancreas a number of facts that are interesting not only in themselves, but doubly so because they promise, when more fully investigated, to throw some light on the manner of consumption of sugar by the tissues. It has been shown by V. Mering and Minkowski[1] and others that if the pancreas of a dog is completely removed, the tissues lose the power of consuming sugar, so that it accumulates in the blood and finally escapes in the urine, causing what has been called "pancreatic diabetes." If a small part of the pancreas is left in the body, even though it is not connected by its duct with the duodenum, diabetes does not occur. The inference usually made from these experiments is that the pancreas gives off something to the blood—an internal secretion—which is necessary to the physiological consumption of sugar. In what way the pancreas exerts this influence has yet to be discovered; possibly it is through the action of a specific enzyme which helps to break down the sugar; possibly it is by some other means. But the necessity of the pancreas in some way for the normal consumption of sugar by the tissues generally seems to be indisputably established. It is a discovery of the utmost importance in its relations to the normal nutrition of the body, and also because of its possible bearing on the pathological condition known as *diabetes mellitus*. In this latter disease the tissues, for some reason, are unable to oxidize the sugar in normal amounts, and a good part of it, therefore, escapes through the urine. The facts and theories bearing upon diabetes are of unusual interest in connection with the nutritive history of the carbohydrates, but for a fuller description reference must be made to more elaborate works.

Another statement in connection with the fate of sugar in the body is worthy of a brief reference: It has been asserted by Lepine and Barral that there is normally present in blood an enzyme capable of destroying sugar. Their theory rests upon the undoubted fact that sugar added to blood outside the body soon disappears. They call the process "glycolysis," and the enzyme to which they attribute this disappearance the "glycolytic enzyme." Others, however (Arthus), have claimed that this enzyme is only a post-mortem result of the disintegration of the corpuscles of the blood, and that it is not present in circulating blood. We must await further investigation upon this point, and be content here with a mere reference to the subject.

Nutritive Value of Water and Salts.—Water is lost daily from the body in large quantities through the kidney, the skin, the lungs, and the feces, and it is replaced by water taken in the food or separately, and partially also by the water formed in the oxidations of the body. A certain percentage of

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[1] *Archiv für experimentelle Pathologie u. Pharmakologie*, 1893, xxxi. p. 85.

water in the tissues and in the liquids of the body is naturally absolutely essential to the normal play of metabolism; and conditions, such as muscular exercise, which increase the water-loss bring about also an increased water-consumption, the regulation being effected through the nervous mechanism which mediates the sensation of thirst. The water taken into the body does not, however, serve directly as a source of energy, since it is finally eliminated in the form in which it is taken in; it serves only to replace water lost from the tissues and liquids of the body, and it furnishes also the menstruum for the varied chemical reactions which take place. Continued deprivation of water leads to intolerable thirst, the cause of which is usually referred to the altered composition of the tissues generally, including the peripheral nervous system.

Inorganic Salts.—The essential value of the inorganic salts to the proper nutrition of the body does not commonly force itself upon our attention, since, as a rule, we get our proper supply unconsciously with our food, without the necessity of making a deliberate selection. NaCl (common table-salt) forms an exception, however, to this rule. Speaking generally, inorganic salts do not serve as a source of energy to the body. Most of the salts found in the urine and other excreta are eliminated in the same form in which they were received into the body. Some of them, however, notably the phosphates and the sulphates, are formed in the course of the metabolism of the tissues, and without doubt reactions of various kinds occur affecting the composition of many of the salts—for example, the decomposition of the chlorides to form the HCl of gastric juice. But these reactions do not materially influence the supply of energy in the body: the value of the salts lies in the general fact that they are necessary to the maintenance of the normal physical and chemical properties of the tissues and the body-fluids. Experimental investigation[1] has shown in a surprising way how immediately important the salts are in this respect. Forster fed dogs and pigeons on a diet in which the saline constituents had been much reduced, although not completely removed. The animals were given proteids, fats, and carbohydrates, but they soon passed into a moribund condition. It seemed, in fact, that the animals died more quickly on a diet poor in salts than if they had been entirely deprived of food. Similar experiments were made by Lunin upon mice, with corresponding results. He showed, moreover, that while mice live very well upon cow's milk alone, yet if given a diet almost free from inorganic salts, consisting of the casein and fats of milk plus cane-sugar, they soon died. Moreover, if all the inorganic salts of milk were added to this diet in the exact proportion in which they exist in the ash of milk, the mixture still failed to support life. It would seem from this result that the inorganic salts cannot fulfil completely their proper functions in the body unless they exist in some special combination with the organic constituents of the food. In this connection it is well to bear in mind that proteids as they occur in nature seem always to be combined with inorganic salts, and the properties of proteids, as we know them, are undoubtedly dependent in part upon the presence of this inorganic constituent.

[1] Bunge: *Physiological and Pathological Chemistry,* translated by Wooldridge, 1890.

It has been shown, for example, that if egg-albumin is completely deprived of its ash, it is no longer soluble in water. We may assume that the original synthesis of the organic and inorganic constituents is made in the plant kingdom, and that, in its own way, the inorganic constituent of the molecule is as necessary to the proper nutrition of the animal tissues as is the organic. One salt (NaCl) is consumed by many animals, including man, in excess of the amount unconsciously ingested with the food. Bunge points out that purely carnivorous animals are not known to crave this salt, while the herbivora with some exceptions—for example, the rabbit—take it at times largely in excess. The need of salt on the part of these animals is well illustrated among the wild forms by the eagerness with which they visit salt-licks. Bunge advances an ingenious theory to account for the difference in regard to the use of salt between the herbivora and the carnivora. He points out that in plant food there is a relatively large excess of potassium salts. When these salts enter the liquids of the body they react with the NaCl present and a mutual decomposition ensues, with the formation of KCl and the sodium salt of the acid formerly combined with the potassium, and the new salts thus formed are eliminated by the kidneys as soon as they accumulate beyond the normal limit. In this way the normal proportion of NaCl in the tissues and the body-fluids is lowered and a craving for the salt is produced. Bunge states that it has been shown among men that vegetarians habitually consume more salt than those who are accustomed to eat meats. The salts of calcium and of iron have also a special importance which needs a word of reference. The particular importance of the iron salts lies in their relation to hæmoglobin. The continual formation of new red blood-corpuscles in the body requires a supply of iron salts for the synthesis of the hæmoglobin, and, although there is a probability (see p. 263) that the iron compound of the disintegrating corpuscles is again used in part for this purpose, we must suppose that the body requires additional iron in the food from time to time to take the place of that which is undoubtedly lost in the excretions. It has been shown that iron is contained in animal and vegetable foods in the form of an organic compound, and the evidence at hand goes to show that only when it is so combined can the iron be absorbed readily and utilized in the body, while the efficacy of the inorganic salts of iron as furnishing directly a material for the production of hæmoglobin is, to say the least, open to doubt. Bunge isolated from the yolk of eggs an iron-containing nuclein which he calls *hæmatogen,* because in the developing hen's egg it is the only source from which the iron required for the production of hæmoglobin can be obtained. It is possible that similar compounds occur in other articles of food. Most of the iron taken with food, however, including that present in the hæmoglobin of meats, passes out in the feces unabsorbed. It is probable that there is an actual excretion of iron from the body, and, so far as known, this excretion is effected in small part through the urine, but mainly through the walls of the intestine, the iron being eliminated finally in the feces. The large proportion of calcium salts found in the skeleton implies a special need of these salts in

the food, particularly in that of the young. It has been shown that if young dogs are fed upon a diet poor in Ca salts, the bones fail to develop properly, and a condition similar to rickets in children becomes apparent. In addition to their relations to bone-formation and the fact that they form a normal constituent of the tissues and liquids of the body, calcium salts are necessary to the coagulation of blood (see p. 355), and, moreover, they seem to be connected in some intimate way with the rhythmic contractility of heart-muscle, and, indeed, with the normal activity of protoplasm in general, animal as well as plant. Notwithstanding the special importance of calcium in the body, no great amount of it seems to be normally absorbed or excreted. Voit has shown that the calcium eliminated from the body is excreted mainly through the intestinal walls, but that most of the Ca in the feces is the unabsorbed Ca of the food. It is possible that the Ca must be present in some special combination in order to be absorbed and utilized in the body. A point of special interest in connection with the nutritive value of the inorganic salts was brought out by Bunge in some analyses of the body-ash of sucking animals in comparison with analyses of the milk and the blood of the mother. In the case of the dog he obtained the following results (mineral constituents in 100 parts of ash):

	Young Pup.	Dog's Milk.	Dog's Serum.
K_2O	8.5	10.7	2.4
Na_2O	8.2	6.1	52.1
CaO	35.8	34.4	2.1
MgO	1.6	1.5	0.5
F_2O_3	0.34	0.14	0.12
P_2O_5	39.8	37.5	5.9
Cl	7.3	12.4	47.6

The remarkable quantitative resemblance between the ash of milk and the ash of the body of the young indicates that the inorganic constituents of milk are especially adapted to the needs of the young; while the equally striking difference between the ash of milk and the ash of the maternal blood seems to show that the inorganic salts of milk are formed from the blood-serum not simply by osmosis, but rather by some selective secretory act. These facts come out most markedly in connection with the CaO and the P_2O_5. For further details as to the history of calcium and iron in the body, consult the section on Chemistry of the Body, under *calcium* and *iron*.

I. ACCESSORY ARTICLES OF DIET; VARIATIONS OF BODY-METABOLISM UNDER DIFFERENT CONDITIONS; POTENTIAL ENERGY OF FOOD; DIETETICS.

Accessory Articles of Diet.—By accessory articles of diet we mean those substances which are taken with food, not for the purpose of replacing tissue or yielding energy, but to add to the enjoyment of eating, to stimulate the appetite, to aid in digestion and absorption, or for some other subsidiary purpose. They include such things as the condiments (mustard, pepper, etc.), the flavors, and the stimulants (alcohol, coffee, tea, chocolate, beef-extracts). They all possess, undoubtedly, a positive nutritive or digestive value beyond contributing to the

mere pleasures of the palate, but their importance is of a subordinate character. They may be omitted from the diet, as happens or may happen in the case of animals, without affecting injuriously the nutrition of the body, although it is probable that neither man nor the lower animals would voluntarily eat food entirely devoid of flavor.

Stimulants.—The well-known stimulating effect of alcohol, tea, coffee, etc. is probably due to a specific action on the nervous system whereby the irritability of the tissue is increased. The physiological effect of tea, coffee, and chocolate is due to the alkaloids caffein (trimethyl-xanthin) and theobromin (dimethyl-xanthin). In small doses these substances are oxidized in the body and yield a corresponding amount of energy, but their value from this standpoint is altogether unimportant compared with their action as stimulants. Alcohol also, when not taken in too large quantities, may be oxidized in the body and furnish a not inconsiderable amount of energy. It is, however, a matter of controversy at present whether alcohol in small doses can be considered a true food-stuff, capable of serving as a direct source of energy and of replacing a corresponding amount of fats or of carbohydrates in the daily diet. The evidence is partly for and partly against such a use of alcohol. For example, Reichert[1] finds that moderate doses of alcohol given to a dog do not affect the heat-production of the body as measured by a calorimeter. Since the alcohol is completely or nearly completely oxidized in the body and gives off considerable heat in the process, the fact that the total heat-production remains unaltered indicates that the oxidation of the alcohol protects an isodynamic amount of proteid or non-proteid material in the body from consumption, thus acting as a food-stuff capable of replacing other elements of the food. On the contrary, Miura[2] has arrived at exactly opposite results in a series of experiments made by another method. In these experiments Miura brought himself into a condition of nitrogen equilibrium upon a mixed diet. Then for a certain period a portion of the carbohydrates was omitted from the diet and its place substituted by an isodynamic amount of alcohol. The result was a loss of proteid from the body, showing that the alcohol had not protected the proteid tissue as it should have done if it acts as a food. In a third period the old diet was resumed, and after nitrogen equilibrium had again been established the same proportion of carbohydrate was omitted from the diet, but alcohol was not substituted. When the diet was poor in proteid, it was found that less proteid was lost from the body when the alcohol was omitted than when it was used, indicating that, so far from protecting the tissues of the body by its oxidation, the alcohol exercised a directly injurious effect upon proteid-consumption. Numerous other researches might be quoted to show that the effect of moderate quantities of alcohol upon body-metabolism is not yet satisfactorily understood. Before making any positive statements as to the details of its action it is wise, therefore, to wait until reliable experimental results have accumulated. The specific action of alcohol on the heart, stomach, and other organs has been investigated more or less completely, but the literature is too great and the results are

[1] *Therapeutic Gazette,* 1890.   [2] *Zeitschrift f. klin. Medicin,* 1892, vol. xx. p. 137.

too uncertain to permit any résumé to be given here. When alcohol is taken in excess it produces the familiar symptoms of intoxication, which may pass subsequently into a condition of stupor or even death, provided the quantity taken is sufficiently great. So, also, the long-continued use of alcohol in large quantities is known to produce serious lesions of the stomach, liver, nerves, blood-vessels, and other organs. The effect of alcohol upon the body evidently varies greatly with the quantity used. It may perhaps be said with safety that in small quantities it is beneficial, or at least not injurious, barring the danger of acquiring an alcohol habit, while in large quantities it is directly injurious to various tissues.

Condiments and Flavors.—These substances probably have a directly bene-ficial effect on the processes of digestion by promoting the secretion of saliva, gastric juice, etc., in addition to the important fact that they increase the pal-atableness of food, and hence increase the desire for food. With reference to the condiments, Brandl has shown, in the paper referred to on p. 252, that mus-tard and pepper also markedly increase the absorption of soluble products from the stomach.

Conditions Influencing Body-metabolism.—In considering the influence of the various food-stuffs upon body-metabolism we have for the most part neglected to mention the effect of changes in the condition of the body. It goes without saying that such things as muscular work, sleep, variations in temperature, etc. have or might have an important effect upon the character and amount of the chemical changes going on in the body, and in conse-quence a great many elaborate investigations have been made to ascertain pre-cisely the effect of conditions such as those mentioned upon the amount of the excretions, the production of heat in the body, and other similar points which throw light upon the nature of the metabolic processes.

Effect of Muscular Work.—It is a matter of common knowledge that mus-cular work increases the amount of food consumed, and therefore the total body-metabolism, but it has been a point in controversy whether the increased oxidations affect the proteid or the non-proteid material. According to Liebig, the source of the energy of muscular work lies in the metabolism of the proteid constituents, and with increased muscular work there should be increased de-struction of proteid and an increase in the nitrogenous excretions. That the total energy of muscular work is not derived from the oxidation or metabolism of proteid alone was clearly demonstrated by the famous experiment of Fick and Wislicenus. These physiologists ascended the Faulhorn to a height of 1956 meters. Knowing the weight of his body, each could estimate how much work was done in ascending such a height. Fick's weight, for example, was 66 kilograms, therefore in climbing the mountain he performed $66 \times 1956 =$ 129,096 kilogrammeters of work. In addition, the work of the heart and the respiratory muscles, which could not be determined accurately, was estimated at 30,000 kilogrammeters. There was, moreover, a certain amount of muscular work performed in the movements of the arms and in walking upon level ground that was omitted entirely from their calculations. For seventeen hours before the ascent, during the climb of eight hours, and for six hours afterward

their food was entirely non-nitrogenous, so that the urea eliminated came entirely from the proteid of the body. Nevertheless, when the urine was collected and the urea estimated it was found that the potential energy contained in the proteid destroyed was entirely insufficient to account for the work done. Although later estimates would modify somewhat the actual figures of their calculation, the margin was so great that the experiment has been accepted as showing conclusively that the total energy of muscular work does not come from the oxidation of proteid alone. Later experiments made by Voit upon a dog working in a tread-wheel and upon a man performing work while in the respiratory chamber (p. 283) gave the surprising result that not only may the energy of muscular work be far greater than the potential energy of the proteid simultaneously oxidized, but that the performance of muscular work within certain limits does not affect at all the amount of proteid metabolized in the body, since the output of urea is the same on working-days as during days of rest. Careful experiments by an English physiologist, Parkes, made upon soldiers while resting and after performing long marches showed also that there is no distinct increase in the excretion of urea after muscular exercise. It follows from these experiments that Liebig's theory as to the source of the energy of muscular work is incorrect, and that the increase in the oxidations in the body which undoubtedly occurs during muscular activity must affect only the non-proteid material, that is, the fats and carbohydrates. Quite recently the question has been reopened by experiments made under Pflüger by Argutinsky.[1] In these experiments the total nitrogen excreted was determined with especial care in the sweat as well as in the urine and the feces. The muscular work done consisted in long walks and mountain-climbs. Argutinsky found that work caused a marked increase in the elimination of nitrogen, the increase extending over a period of three days, and he estimated that the additional proteid metabolized in consequence of the work was sufficient to account for most of the energy expended in performing the walks and climbs. A number of objections have been made to Argutinsky's work. It has been asserted that during his experiment he kept himself upon a diet deficient in non-proteid material; that if the supply of this material had been sufficient, none of the additional proteid would have been oxidized. It must be admitted, however, that the experiments of Argutinsky compel us to state the proposition above as to the relation between muscular work and proteid metabolism in a more careful way. It is necessary to modify the statement generally made to the extent of saying that muscular work causes no increase in proteid metabolism, provided the supply of food is abundant.

If now we compare the amounts of CO_2 eliminated during work and during rest, it will be found that there is a very decided increase during work. In the experiments made by Pettenkofer and Voit the CO_2 given off by a man during a day of muscular work was nearly double that eliminated during a resting-day. Indeed, the same fact has been observed repeatedly upon isolated muscles made to contract by artificial stimuli. Assuming, then, that muscular

[1] *Pflüger's Archiv für die gesammte Physiologie*, 1890, vol. 46, p. 552.

work causes no increase in the nitrogen excreted, but a marked increase in the CO_2 eliminated, we are justified in saying that the energy of muscular work under normal conditions comes mainly, if not exclusively, from the oxidation of non-proteid material. The machine that does the work, the muscle, is *par excellence* a proteid tissue, but the normal resting metabolism of its proteid substance is not increased by the chemical changes of contraction. Or, to put it in another way, the chemical changes which give rise to the energy liberated in contraction involve only the non-proteid material. It is interesting to remember in this connection that the consumption of glycogen, or of the sugar derived from it, is intimately connected with muscular work. The glycogen of the body in an animal deprived of food disappears much more rapidly if the animal is made to work his muscles than if he remains at rest. In an experiment by Külz upon well-fed dogs it was found that the glycogen was practically all used up in a single fasting-day during which the animals did a great deal of work. Morat and Dufourt have shown also that a muscle after prolonged contraction takes much more sugar from the blood than it did previous to the contraction, and Harley[1] finds that power to perform muscular work may be increased and susceptibility to fatigue be diminished by eating sugar in quantities. It is, in fact, generally agreed that glycogen is used up in muscle-contractions, but the way in which the destruction of the glycogen is effected is not definitely known. After the glycogen has been consumed it is probable that the other constituents of the body, the fats and the proteids, are called upon to furnish the necessary energy. For this reason we should expect, in a person performing excessive muscular work, that there would be an increased destruction of proteid when the supply of non-proteid food is insufficient.

Metabolism during Sleep.—It has been shown that during sleep there is no marked diminution of the nitrogen excreted, and therefore no distinct decrease in the proteid metabolism; on the contrary, the CO_2 eliminated and the oxygen absorbed are unquestionably diminished. This latter fact finds its simplest explanation in the supposition that the muscles are less active during sleep. The muscles do less work in the way of contractions, and, in addition, probably suffer a diminution in tonicity which also affects their total metabolism.

Effect of Variations in Temperature.—In warm-blooded animals variations of outside temperature within ordinary limits do not affect the body-temperature. A full account of the means by which this regulation is effected will be found in the section upon Animal Heat. So long as the temperature of the body remains constant, it has been found that a fall of outside temperature increases the oxidation of non-proteid material in the body, the increase being in a general way proportional to the fall in temperature. That the increased oxidation affects the non-proteid constituents is shown by the fact that the urea remains unchanged in quantity, other conditions being the same, while the oxygen-consumption and the CO_2-elimination are increased. A

[1] *Journal of Physiology*, 1894, vol. xvi. p. 97.

rise of outside temperature has naturally the opposite effect : oxygen-consumption and CO_2-elimination are diminished. This effect of temperature upon the body-metabolism is due mainly to a reflex stimulation of the motor nerves to the muscles. The temperature-nerves of the skin are affected by the rise or fall in outside temperature, and bring about reflexly an increased or a diminished innervation of the muscles of the body. The fact that variations in outside temperature affect only the consumption of non-proteid material falls in, therefore, with the conception of the nature of the metabolism of muscle in activity, given above. When the means of regulating the body-temperature break down from too long an exposure to excessively low or excessively high temperatures, the total body-metabolism, proteid as well as non-proteid, increases with a rise in body-temperature and decreases with a fall in temperature. In fevers arising from pathological causes it has been shown that there is also an increased production of urea as well as of CO_2.

Effect of Starvation.—A starving animal must live upon the material present in its body. This material consists of the fat stored up, the circulating and tissue proteid, and the glycogen. The latter, which is present in comparatively small quantities, is quickly used, disappearing more or less rapidly according to the extent of muscular movements made, although in any case it practically vanishes in a few days. Thereafter the animal lives on its own proteid and fat, and if the starvation is continued to a fatal termination the body becomes correspondingly emaciated. Examination of the several tissues in animals starved to death has brought out some interesting facts. Voit took two cats of nearly equal weight, fed them equally for ten days, and then killed one to serve as a standard of comparison and starved the other for thirteen days : the latter animal lost 1017 grams in weight, and the loss was divided as follows among the different organs :

	Actual loss (in fresh organ).	Loss to each 100 grams (fresh organ).
Bone	55 grams.	14 grams.
Muscle	429 "	31 "
Liver	49 "	54 "
Kidney	7 "	26 "
Spleen	6 "	67 "
Pancreas	1 "	17 "
Testis	1 "	40 "
Lung	3 "	18 "
Heart	0 "	3 "
Intestine	21 "	18 "
Brain and cord	1 "	3 "
Skin and hair	89 "	21 "
Fat	267 "	97 "
Blood	37 "	27 "

According to these results, the greatest absolute loss was in the muscles (429 grams), while the greatest percentage loss was in the fat (97 per cent.), which had practically disappeared from the body. It is very significant that the central nervous system and the heart, organs which we may suppose were in continual activity, suffered no loss of weight: they had lived at the expense of

the other tissues.   We must suppose that in a starving animal the fat and the proteid material, particularly that of the voluntary muscles, pass into solution in the blood, and are then used to nourish the tissues generally and to supply the heat necessary to maintain the body-temperature.   Examination of the excreta in starving animals has shown that a greater quantity of proteid is destroyed during the first day or two than in the subsequent days.   This fact is explained on the supposition that the body is at first richly supplied with "circulating proteid" derived from its previous food, and that after this is metabolized the animal lives entirely, so far as proteid-consumption is concerned, upon its "tissue proteid."   The general fact that the loss of proteid is greatest during the first one or two days of starvation has been confirmed recently upon men, in a number of interesting experiments made upon professional fasters.   For the numerous details as to loss of weight, variations of temperature, etc., carefully recorded in these latter experiments, reference must be made to original sources.[1]   It may be added, in conclusion, that the fatter the body is to begin with, the longer will starvation be endured, and that if water is consumed freely the evil effects of starvation, as well as the disagreeable sensations of hunger, are very much reduced.

Potential Energy of Food.—The chemical changes occurring in the body are accompanied by a liberation of energy in different forms—for example, as heat, electricity, and mechanical work.   By far the most of this energy takes the form, directly or indirectly, of heat.   Even when the muscles are apparently at rest we know that they are undergoing chemical changes which give rise to heat.   When a muscle contracts, the greater part (four-fifths) of the energy liberated by the chemical change takes the form of heat; a much smaller part (about one-fifth as a maximum) may perform mechanical work, which in turn, as in the case of the respiratory muscles and the heart, may be converted to heat within the body.   Roughly speaking, an adult man gives off from his body in the course of twenty-four hours about 2,400,000 calories of heat (1 calorie = the heat necessary to raise 1 cubic centimeter of water 1° C.).   This supply of heat is derived from the metabolism or physiological oxidation of the proteids, the fats, and the carbohydrates which we take into the body in our food.   By means of the oxygen absorbed through the lungs these substances are burnt, with the formation of CO_2, H_2O, and urea or some similar nitrogenous waste product.   In the long run, then, the source of body-energy is found in the potential energy contained in our food.   Our energy-yielding foods—proteids, fats, and carbohydrates—are more or less complex bodies which are built up originally by plant organisms with the consumption of solar energy; when they are burnt or otherwise destroyed, with the formation of simpler bodies (such as CO_2 or H_2O), the contained potential energy is liberated in the form of heat, and this is what occurs in the body.   From the standpoint of the law of conservation of energy it is easy to understand that the amount of available energy in any food-stuff may be determined by burning it outside the body and measuring the quantity of heat liberated.   If a gram of sugar is

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[1] Virchow's *Archiv*, vol. 131, supplement, 1893, and Luciani, *Das Hungern*, 1890.

burnt, it is converted to CO_2 and H_2O and a certain quantity of heat is liberated; if the same gram of sugar had been taken into the body, it would eventually have been reduced to the form of CO_2 and H_2O, and the total quantity of heat liberated would have been the same as in the combustion outside the body, although the destruction of the sugar in the body may not be a direct, but an indirect, oxidation; that is, the oxygen may first be combined with sugar and other food-stuffs to form a complex molecule which afterward dissociates into simpler compounds similar to those obtained by direct oxidation, or there may be first a dissociation or cleavage followed by oxidation of the dissociation products. In determining the total energy given to the body we need only consider the form in which a substance enters the body and the form in which it is finally eliminated. In the case of proteids the combustion in the body is not so complete as it is outside; the final products are CO_2, H_2O, and urea; the urea, however, still contains potential energy which may be liberated by combustion, and in determining the energy of proteid available to the body, that which is lost in the urea must be deducted. As a matter of fact, there is some evidence (see origin of urea, p. 276) to show that proteid in the body is completely oxidized to CO_2, H_2O, and NH_3; but, since the NH_3 in this case recombines with a part of the CO_2 and the H_2O to form ammonium carbamate, and this in turn is converted into urea, the additional energy liberated in the first combustion is balanced by that absorbed in the synthetic production of the urea. The potential energy of the fats, carbohydrates, and proteids can be determined by combustion outside the body ; the energy liberated is measured in terms of heat by some form of calorimeter, and the quantity of heat so obtained, expressed in calories, is known usually as the "combustion equivalent." To be perfectly accurate, each particular form of fat, proteid, etc. should be burnt and its energy be determined, but usually average figures are employed, as the amount of heat given off by the different varieties of any one food-stuff—proteids, for example—does not vary greatly. According to Stohmann, 1 gram of beef deprived of fat = 5641 calories, while 1 gram of veal gives 5663 calories. For muscle extracted with water, Rubner obtained the following figures: 1 gram = 5778 calories. The combustion equivalent of urea (Rubner) is 2523 calories. Since 1 gram of proteid yields about one-third of a gram of urea, we must deduct 841 calories from the combustion equivalent of one gram of proteid to get its available energy to the body: 5778 — 841 = 4937 calories. The combustion equivalents of fats and carbohydrates, as given by Stohmann, are: 1 gram of fat = 9312 calories; 1 gram of starch = 4116 calories. Weight for weight, fat contains the most energy, and, as we know, in cold weather and in cold climates the proportion of fat in the food is increased. In dietetics, however, the use of fat is limited by the difficulty attending its digestion and absorption as compared with carbohydrates. Fats and carbohydrates have the same general nutritive value to the body: they serve to supply energy. Since the amount of potential energy contained in each of these substances may be determined accurately by means of its combustion equivalent, it would seem probable that they might be mutually

interchangeable in dietetics in the ratio of their combustion equivalents. Such, in fact, is the case. The ratio of interchange is known as the "iso-dynamic equivalent," and it is given usually as 1 : 2.4 or 2.2 ; that is, fats may replace over twice their weight of carbohydrate in the diet. It follows from the general principles just stated that if we wished to know the amount of heat produced in the body in a given time, say twenty-four hours, we might ascertain it in one of two ways : In the first place, the animal might be placed in a calorimeter and the heat given off in twenty-four hours be measured directly. This method, which is that of direct calorimetry, is described more completely in the section treating of Animal Heat. Secondly, one might feed the animal upon a diet containing known quantities of proteid, fats, and carbohydrates, and by collecting the total N and C excreta determine how much of each of these had been destroyed in the body. Knowing the combustion equivalent of each, the total quantity of heat liberated in the body could be ascertained. This latter method is known as indirect calorimetry. The two methods, if applied simultaneously to the same animal, should give identical results. It is very interesting to know that an experiment of this character has been successfully performed by Rubner ;[1] his experiments were made with the greatest accuracy and with careful attention to all the possible sources of error, and it was found that the quantities of heat as determined by the two methods agreed to within less than 0.5 per cent. These experiments are note-worthy because they furnish us with the first successful experimental demon-stration of the accuracy of the general principles, stated above, upon which the available energy of foods is calculated.

Dietetics.—The subject of the proper nourishment of individuals or col-lections of individuals—armies, inmates of hospitals, asylums, prisons, etc.—is treated usually in books upon hygiene, to which the reader is referred for practical details. The general principles of dieting have been obtained, how-ever, from experimental work upon the nutrition of animals. These principles have been stated more or less completely in the foregoing pages, but some additional facts of importance may be referred to conveniently at this point. In a healthy adult who has attained his maximum weight and size the main object of a diet is to furnish sufficient nitrogenous and non-nitrogenous food-stuffs, together with salts and water, to maintain the body in equilibrium—that is, to prevent loss of proteid tissue, fat, etc. In speaking of the nutritive value of the food-stuffs it was shown that in carnivora (dogs) this condition of equilibrium may be maintained upon proteid food alone, putting aside all consideration of salts and water, or upon proteids and fats, or upon proteids and carbohydrates, or upon proteids, fats, and carbohydrates. When proteids alone are used, the quantity must be increased far above that necessary in the case of a mixed diet, and it is doubtful whether, in the case of man or the herbivora, a healthy nutritive condition could be maintained long upon such a diet, owing to the largely increased demand upon the power of the alimentary canal to digest and absorb proteids, to the greater labor thrown on the kidneys, etc.

[1] *Zeitschrift für Biologie,* 1893, vol. xxx. p. 73.

The experience of mankind, as well as the results of experimental investigation, shows that the healthy diet is one composed of proteids, fats, and carbohydrates. The proportion in which the fats and the carbohydrates should be taken—and, to a certain extent, this is true also of the proteids—may be varied within comparatively wide limits, in accordance with the law of "isodynamic equivalents." This is illustrated by the following "average diets" calculated by different physiologists to indicate the average amount of food-stuffs required by an adult man under normal conditions of life:

Average Diets.

	Moleschott.	Ranke.	Voit.	Forster.	Atwater.
Proteid	130 grams.	100 grams.	118 grams.	131 grams.	125 grams.
Fats	40 "	100 "	56 "	68 "	125 "
Carbohydrates	550 "	240 "	500 "	494 "	400 "

In Voit's diet, which is the one usually taken to represent the daily needs of the body, it will be noticed that the ratio of the nitrogenous to the non-nitrogenous food-stuffs is about as 1 : 5. It must be remembered, in regard to these diets, that the amounts of food-stuffs given refer to the dry material: 118 grams of proteid do not mean 118 grams of lean meat, for example, since lean meat (flesh) contains a large proportion of water. Tables of analyses of food (one of which is given on page 216) enable us to determine for each particular article of food the proportion of dry food-stuffs contained in it, and in how great quantities it must be taken to furnish the requisite amount of proteid, fats, or carbohydrates. There is, however, still another practical consideration which must be taken into account in estimating the nutritive value of articles of food from the analyses of their composition, and that is the extent to which each food-stuff in each article of food is capable of being digested and absorbed. Practical experience has shown that proteids in certain articles of food can be digested and absorbed nearly completely when not fed in excess, while in other foods only a certain percentage of the proteid is absorbed under the most favorable conditions. This difference in usableness of the food-stuffs in various foods is most marked in the case of proteids, but it occurs also with the fats and the carbohydrates. Facts of this kind cannot be determined by mere analysis of the foods; they must be obtained from actual feeding experiments upon man or the lower animals. In general, it may be said that in meats from 2 to 3 per cent., in milk from 6 to 12 per cent., and in vegetables from 10 to 40 per cent. of the proteid escapes absorption. The greater value of the meats, then, as a source of proteid supply consists not only in the greater average percentage of proteid contained in them as compared with the vegetables, but also in the fact that their proteid is more completely absorbed from the alimentary canal, less being lost in the feces. Munk [1] gives an interesting table showing how much of certain familiar articles of food would be necessary, if taken alone, to supply the requisite daily amount of proteid or non-proteid food; his

[1] Weyl's *Handbuch der Hygiene*, 1893, vol. iii., part i. p. 69.

estimates are based upon the percentage composition of the foods and upon experimental data showing the extent of absorption of the food-stuffs in each food. In this table he supposes that the daily diet should contain 110 grams proteid = 17.5 grams of N, and non-proteids sufficient to contain 270 grams of C :

	For 110 grams proteid (17.5 grams N).	For 270 grams C.
Milk	2900 grams.	3800 grams.
Meat (lean)	540 "	2000 "
Hen's eggs	18 eggs.	37 eggs.
Wheat flour	800 grams.	670 grams.
Wheat bread	1650 "	1000 "
Rye bread	1900 "	1100 "
Rice	1870 "	750 "
Corn	990 "	660 "
Peas	520 "	750 "
Potatoes	4500 "	2550 "

As Munk points out, this table shows that any single food, if taken in quantities sufficient to supply the nitrogen, would give too much or too little C, and the reverse; those animal foods which, in certain amounts, supply the nitrogen needed furnish only from one-quarter to two-thirds of the necessary amount of C. To live for a stated period upon a single article of food—a diet sometimes recommended to reduce obesity—means, then, an insufficient quantity of either N or C and a consequent loss of body-weight. Such a method of dieting amounts practically to a partial starvation. In practical dieting we are accustomed to get our supply of proteids, fats, and carbohydrates from both vegetable and animal foods. To illustrate this fact by an actual case, in which the food was carefully analyzed, an experimenter (Krummacher) weighing 67 kilograms records that he kept himself in N equilibrium upon a diet in which the proteid was distributed as follows :

300 grams meat	=	63.08 grams proteid	=	9.78 grams N.
666.3 c.c. milk	=	18.74 " "	=	2.905 " "
100 grams rice	=	7.74 " "	=	1.2 " "
100 " bread	=	11.32 " "	=	1.755 " "
500 c.c. wine	=	1.17 " "	=	0.182 " "
		102.05 " "	=	15.868 " "

For a person in health and leading an active normal life, appetite and experience seem to be safe and sufficient guides by which to control the diet; but in conditions of disease, in regulating the diet of children and of collections of individuals, scientific dieting, if one may use the phrase, has accomplished much, and will be of greater service as our knowledge of the physiology of nutrition increases.

V. MOVEMENTS OF THE ALIMENTARY CANAL, BLADDER, AND URETER.

PLAIN MUSCLE-TISSUE.

THE movements of the alimentary canal and the organs concerned in micturition are effected for the most part through the agency of - plain muscletissue. The general properties of this tissue have been referred to in the section upon the Physiology of Muscle and Nerve, but it seems appropriate in this connection to again call attention to some points in its general physiology and histology, inasmuch as the character of the movements to be described depends so much upon the fundamental properties exhibited by this variety of muscle-tissue. Plain muscle as it is found in the walls of the abdominal and pelvic viscera is composed of masses of minute spindle-shaped cells whose size is said to vary from 22 to 560 μ in length and from 4 to 22 μ in width, the average size, according to Kölliker, being 100 to 200 μ in length and 4 to 6 μ in width. Each cell has an elongated nucleus, and its cytoplasm shows a longitudinal fibrillation. Cross striation, such as occurs in cardiac and striped muscle, is absent. These cells are united into more or less distinct bundles or fibres, which run in a definite direction corresponding to the long axes of the cells. The bundles of cells are united to form flat sheets of muscle of varying thicknesses, which constitute part of the walls of the viscera and are distinguished usually as longitudinal and circular muscle-coats according as the cells and bundles of cells have a direction with or at right angles to the long axis of the viscus. The constituent cells are united to one another by cementsubstance, and according to several observers[1] there is a direct protoplasmic continuity between neighboring cells—an anatomical fact of interest, since it makes possible the conduction of a wave of contraction directly from one cell to another. Plain muscle-tissue, in some organs at least, e. g. the stomach, intestines, bladder, and arteries, is under the control of motor nerves. There must be, therefore, some connection between the nerve-fibres and the muscletissue. The nature of this connection is not definitely established; according to Miller[2] the nerve-fibres terminate eventually in fine nerve-fibrils which run in the cement-substance between the cells and send off small branches which end in a swelling applied directly to the muscle-cell. Berkley[3] finds a similar

[1] See Boheman: *Anatomischer Anzeiger*, 1894, Bd. 10, No. 10.
[2] *Archiv für mikroskopische Anatomie*, 1892, Bd. 40.
[3] *Anatomischer Anzeiger*, 1893, Bd. 8.

ending of the nerves, and in addition describes in the muscularis mucosæ of the intestine a large globular end-organ which he considers as a motor plate.

Perhaps the most striking physiological peculiarity of plain muscle, as compared with the more familiar striated muscle, is the sluggishness of its contractions. Plain muscle, like striated muscle, is independently irritable. Various forms of artificial stimuli, such as electrical currents, mechanical, chemical, and thermal stimuli, may cause the tissue to contract when directly applied to it, but the contraction in all cases is characterized by the slowness with which it develops. There is a long latent period, a gradual shortening which may persist for some time after the stimulus ceases to act, and a slow relaxation. These features are represented in the curve shown in Figure 81, which it is instructive to compare with the typical curve of a striated muscle (Fig. 34). The slowness of the contraction of plain muscle seems to depend upon the absence of cross striation. Striped muscle as found in various animals or in different muscles of the same animal—e. g. the pale and red muscles of the rabbit—differs greatly in the rapidity of its contraction, and it has been shown that the more perfect the cross striation the more rapid is the contraction. The cross striation, in other words, is the expression of a mechanism or structure adapted to quick contractions and relaxations, and the relatively great slowness of movement in the plain muscle seems to result from the absence of this particular structure. It should be added, however, that plain muscle in different parts of the body exhibits considerable variation in the rapidity with which it contracts under stimulation, the ciliary muscle of the eyeball, for example, being able to react more rapidly than the muscles of the intestines. The gentle prolonged contraction of the plain muscle is admirably adapted to its function in the intestine of moving the food-contents along the canal with sufficient slowness to permit normal digestion and absorption. Like the striated muscle, and unlike the cardiac muscle, plain muscle is capable of
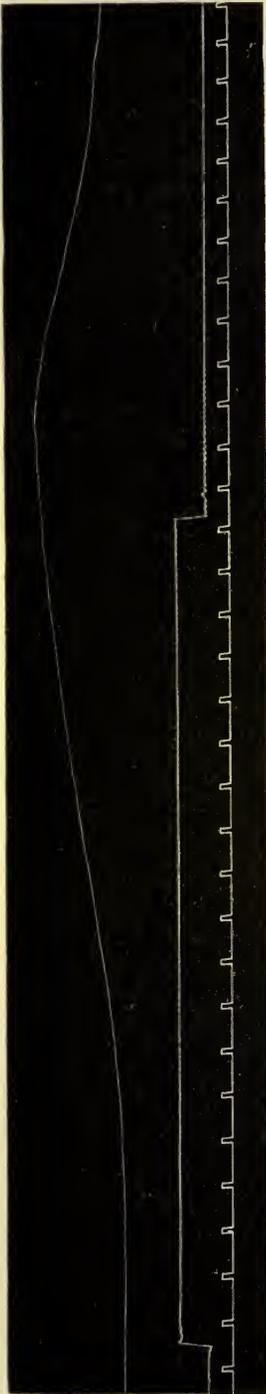
FIG. 85.—Contraction of a strip of plain muscle from the stomach of a terrapin. The bottom line gives the time-record in seconds; the middle line shows the time of application of the stimulus, a tetanizing current from an induction coil; the upper line is the curve recorded by the contracting muscle.

giving submaximal as well as maximal contractions; with increased strength of stimulation the amount of the shortening increases until a maximum is reached. This fact may be observed not only upon isolated strips of muscle from the stomach, but may be seen also in the different degrees of contraction exhibited by the intestinal musculature as a whole when acted upon by various stimuli.

In his researches upon the movements of the ureter Engelmann[1] showed that a stimulus applied to the organ at any point caused a contraction which starting from the point stimulated might spread for some distance in either direction. Engelmann interprets this to mean that the contraction wave in the case of the ureter is propagated directly from cell to cell, and this possibility is supported by the fact, before referred to, that there is direct protoplasmic continuity between adjoining cells. This passage of a contraction wave from cell to cell has, in fact, often been quoted as a peculiarity of plain muscle-tissue. In the case of the ureter the fact seems to be established, but in the intestines, where there is a rich intrinsic supply of nerve-ganglia, it is not possible to demonstrate clearly that the same property is exhibited. The wave of contraction in the intestine following artificial stimulation is, according to most observers, usually localized at the point stimulated or is propagated in only one direction, and these facts are difficult to reconcile with the hypothesis that each cell may transmit its condition of activity directly to neighboring cells. Upon the plain muscle of the ureter Engelmann was able to show also an interesting resemblance to cardiac muscle, in the fact that each contraction is followed by a temporary diminution in irritability and conductivity; but this important property, which in the case of the heart has been so useful in explaining the rhythmic nature of its contractions, has not been demonstrated for all varieties of plain muscle occurring in the body.

A general property of plain muscle which is of great significance in explaining the functional activity of this tissue is exhibited in the phenomenon of "tone." By tone or tonic activity as applied to muscle-tissue is meant a condition of continuous contraction or shortening which persists for long periods and may be slowly increased or decreased by various conditions affecting the muscle. Both striated and cardiac muscle exhibit tone, and in the latter at least the condition is independent of any inflow of nerve-impulses from the extrinsic nerves. Plain muscle exhibits the property in a marked degree. The muscular coats of the alimentary canal, the blood-vessels, the bladder, etc., are usually found under normal circumstances in a condition of tone which varies from time to time and differs from an ordinary visible contraction in the slowness with which it develops and in its persistence for long periods. Such conditions as the reaction of the blood, for example, are known to alter greatly the tone of the blood-vessels, a less alkaline reaction than normal causing relaxation, while an increase in alkalinity favors the development of tone. Tone may also be increased or diminished by the action of motor or inhibitory

[1] *Pflüger's Archiv für die gesammte Physiologie*, 1869, Bd. 2, S. 243.

nerve-fibres, but the precise relationship between the changes underlying the development of tone and those leading to the formation of an ordinary contraction has not been satisfactorily determined.

The mode of contraction of the plain muscle in the walls of some of the viscera, especially the intestine and ureter, is so characteristic as to be given the special name of peristalsis. By peristalsis, or vermicular contraction as it is sometimes called, is meant a contraction which, beginning at any point in the wall of a tubular viscus, is propagated along the length of the tube in the form of a wave, each part of the tube as the wave reaches it passing slowly into contraction until the maximum is reached, and then gradually relaxing. In viscera like the intestine, in which two muscular coats are present, the longitudinal and the circular, the peristalsis may involve both layers, either simultaneously or successively, but the striking feature observed when watching the movement is the contraction of the circular coat. The contraction of this coat causes a visible constriction of the tube, which may be followed by the eye as it passes onward.

MASTICATION.

Mastication is an entirely voluntary act. The articulation of the mandibles with the skull permits a variety of movements ; the jaw may be raised and lowered, may be projected and retracted, or may be moved from side to side, or various combinations of these different directions of movement may be effected. The muscles concerned in these movements and their innervation are described as follows : The masseter, temporal and internal pterygoids raise the jaw ; these muscles are innervated through the inferior maxillary division of the trigeminal. The jaw is depressed mainly by the action of the digastric muscle, assisted in some cases by the mylo-hyoid and the genio-hyoid. The two former receive motor-fibres from the inferior maxillary division of the fifth cranial, the last from a branch of the hypoglossal. The lateral movements of the jaws are produced by the external pterygoids, when acting separately. Simultaneous contraction of these muscles on both sides causes projection of the lower jaw. In this latter case forcible retraction of the jaw is produced by the contraction of a part of the temporal muscle. The external pterygoids also receive their motor fibres from the fifth cranial nerve, through its inferior maxillary division. The grinding movements commonly used in masticating the food between the molar teeth are produced by a combination of the action of the external pterygoids, the elevators, and perhaps the depressors. At the same time the movements of the tongue and of the muscles of the cheeks and lips serve to keep the food properly placed for the action of the teeth, and to gather it into position for the act of swallowing.

DEGLUTITION.

The act of swallowing is a complicated reflex movement which may be initiated voluntarily, but is for the most part completed quite independently

of the will. The classical description of the act given by Magendie divides it into three stages, corresponding to the three anatomical regions, the mouth, pharynx and œsophagus, through which the swallowed morsel passes on its way to the stomach. The first stage consists in the passage of the bolus of food through the isthmus of the fauces—that is, the opening lying between the ridges formed by the palato-glossi muscles, the so-called anterior pillars of the fauces. This part of the act is usually ascribed to the movements of the tongue itself. The bolus of food lying upon its upper surface is forced backward by the elevation of the tongue against the soft palate from the tip toward the base. This portion of the movement may be regarded as voluntary, to the extent at least of manipulating the food into its proper position on the dorsum of the tongue, although it is open to doubt whether the entire movement is usually effected by a voluntary act. Under normal conditions the presence of moist food upon the tongue seems essential to the complete execution of the act; and an attempt to make the movement with very dry material upon the tongue is either not successful or is performed with difficulty. The second act comprises the passage of the bolus from the isthmus of the fauces to the œsophagus —that is, its transit through the pharynx. The pharynx being a common passage for the air and the food, it is important that this part of the act should be consummated quickly. According to the usual description the motor power driving the bolus downward through the pharynx is derived from the contraction of the pharyngeal muscles, particularly the constrictors, which contract from above downward and drive the food into the œsophagus. Simultaneously, however, a number of other muscles are brought into action, the general effect of which is to shut off the nasal and laryngeal openings and thus prevent the entrance of food into the corresponding cavities. The whole reflex is therefore an excellent example of a finely co-ordinated movement.

The following events are described: The mouth cavity is shut off by the position of the tongue against the soft palate and by the contraction of the muscles of the anterior pillars of the fauces. The opening into the nasal cavity is closed by the elevation of the soft palate (action of the levator palati and tensor palati muscles) and the contraction of the posterior pillars of the fauces (palato-pharyngei muscles) and the elevation of the uvula (azygos uvulæ muscle). The soft palate, uvula, and posterior pillars thus form a sloping surface shutting off the nasal chamber and facilitating the passage of the food backward into the pharynx where the constrictor muscles may act upon it. The respiratory opening into the larynx is closed by the adduction of the vocal cords (lateral crico-arytenoids and constrictors of the glottis) and by the elevation of the entire larynx and a depression, in part mechanical, of the epiglottis over the larynx (action of the thyro-hyoids, digastrics, genio-hyoids, and mylo-hyoids and the muscles in the aryteno-epiglottidean folds). The movements of the epiglottis during this stage of swallowing have been much discussed. The usual view is that it is pressed down upon the laryngeal orifice like the lid of a box and thus effectually protects the respiratory passage. It has been shown, however, that removal of the epiglottis does not prevent normal swallowing,

and recently Stuart and McCormick [1] have reported the case of a man in whom part of the pharynx had been permanently removed by surgical operation and in whom the epiglottis could be seen during the act of swallowing. In this individual, according to their observations, the epiglottis was not folded back during swallowing, but remained erect. Later observations by Kanthack and Anderson,[2] made partly upon themselves and partly upon the lower animals, tend, on the contrary, to support the older view. They state that in normal individuals the movement of the epiglottis backward during swallowing may be felt by simply passing the finger back into the pharynx until it comes into contact with the epiglottis. At the beginning of the movement there is also a contraction of the longitudinal muscles of the pharynx which tends to pull the pharyngeal walls toward the bolus of food while, as has been said, the nearly simultaneous contraction of the constrictors presses upon the food and forces it downward. The food is thus brought quickly into the opening of the œsophagus and the third stage commences.

The transit of the food through the œsophagus is effected by the action of its intrinsic musculature. The muscular coat is arranged in two layers, an external longitudinal and an internal circular. These are composed of plain muscle-tissue in the lower third or two-thirds of the œsophagus, but in most mammals the upper third or more contains striated muscular tissue. The chief factor in the transportation of the bolus through the œsophagus has been supposed to consist in the contraction of the circular muscle. This contraction begins at the pharyngeal opening of the œsophagus and passes downward in the form of a wave, peristaltic contraction, which moves rapidly in the upper segment where the musculature is striated, and more slowly in the lower segments in accordance with the physiological characteristics of plain muscle. The result of this movement would naturally be to force the food onward to the stomach. The longitudinal muscles of the œsophagus are without doubt brought into action at the same time, but in this as in other cases of peristalsis in tubular viscera it is not perfectly clear how they co-operate in producing the onward movement. It may be that their contraction slightly precedes that of the circular muscle, and thus tends to dilate the tube and to bring it forward over the bolus. At the opening of the œsophagus into the stomach, the cardiac orifice, the circular fibres of the œsophagus function as a sphincter which is normally in a condition of tone, particularly when the stomach contains food, and thus shuts off the cavity of the stomach from the œsophagus. In swallowing, however, the advancing peristaltic wave has sufficient force to overcome the tonicity of the sphincter, and possibly there is at this moment a partial inhibition of the sphincter. In either case the result is that the food is forced through the narrow opening into the stomach with sufficient energy to give rise to a sound which may be heard by auscultation over this region.[3] According to measurements by Kronecker and Meltzer the entrance of the

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[1] *Journal of Anatomy and Physiology,* 1892.

[2] *Journal of Physiology,* 1893, vol. xiv. p. 154.

[3] See Meltzer: *Centralblatt für die med. Wissenschaften,* 1881, No. 1.

food into the stomach occurs in man about six seconds after the beginning of the act of swallowing.

Kronecker-Meltzer Theory of Deglutition.—The usual view of the mechanism of swallowing has been seriously modified by Kronecker and Meltzer.[1] The experiments of these observers seem to be so conclusive that we must believe that in the main their explanation of the process is correct. According to their view the chief factor in forcing soft or liquid food through the pharynx and œsophagus is the sharp and strong contraction of the mylo-hyoid muscles. The bolus of food lies upon the dorsum of the tongue and by the pressure of the tip of the tongue against the palate it is shut off from the front part of the mouth-cavity. The mylo-hyoids now contract, and the bolus of food is put under high pressure and is shot in the direction of least resistance—namely, through the pharynx and œsophagus. This effect is aided by the simultaneous contractions of the hyoglossi muscles, which tend to still further increase the pressure upon the food by moving the tongue backward and downward. This same movement of the tongue suffices also to depress the epiglottis over the larynx, and thus protect the respiratory opening. By means of small rubber bags connected with recording tambours, which were placed in the pharynx and at different levels in the œsophagus, they were able to demonstrate the rapid spirting of the food through the whole length of pharynx and œsophagus, the time elapsing between the beginning of the swallowing movement and the arrival of the food at the cardiac orifice of the stomach being not more than 0.1 second. The contraction of the constrictors of the pharynx and the peristaltic wave along the œsophagus, according to this view, normally follow after the food has been swallowed, and may be regarded as a movement in reserve which is useful in removing adherent fragments along the deglutition passage, or possibly, in case of the failure of the first swallowing act from any cause—as may result, for instance, in swallowing food too dry or too solid—serves to actually push the bolus downward, although at a much slower rate. From auscultation of the deglutition sound which ensues when the food enters the stomach through the cardia, Kronecker and Meltzer believe that usually the swallowed food after reaching the end of the œsophagus is kept from entering the stomach by the tonic contraction of the sphincter at that point, until the subsequent peristaltic wave of the œsophagus, which reaches the same point in about six seconds after the beginning of the act of swallowing, forces it through. There are, however, exceptions to this rule. In some persons, apparently, the food is forced into the stomach by the energy of the first contraction of the mylo-hyoid muscles. The difference would seem to depend upon the condition of the sphincter at the cardiac orifice. Moreover, these authors were able to determine by their method of recording that the human œsophagus contracts apparently in three successive segments. The first of these comprises about six centimeters in the neck region, and its contraction begins about 1 or 1.2 seconds after the beginning of swallowing and is comparatively short, lasting 2 seconds, corresponding to the

[1] *Du Bois-Reymond's Archiv für Physiologie*, 1883, Suppl. Bd., S. 328.

striated character of the muscle. The second segment covers about ten centi-
meters of the upper thoracic portion of the œsophagus; its contraction begins
about 1.8 seconds after the beginning of the contraction of the first segment,
and is longer, lasting 6 to 7 seconds. The third segment includes the
remainder of the œsophagus; its contraction begins about 3 seconds after the
contraction of the second segment, and lasts a much longer time, about 9–10
seconds. These figures apply, of course, to a single act of swallowing. It
will be seen that according to these authors the swallowing reflex consists
essentially in the successive contractions of five muscular segments or bands—
namely, the mylo-hyoids, the constrictors of the pharynx, and the three seg-
ments of the œsophagus described. The time elapsing between the contractions
of these successive parts was determined as follows :

From the beginning of the contraction of the mylo-hyoids to that of the
    constrictors of the larynx . . . . 0.3 second.
From the beginning of the contraction of the constrictors to that of
    the first œsophageal segment . . . . 0.9   "
Between the first and second œsophageal segments . . . . 1.8 seconds.
    "   " second and third   "   "   . . . . 3.0   "

The total time before the wave of contraction reaches the stomach would
be therefore, as has been stated, about six seconds. When a second act of
swallowing is made within six seconds of the first swallow it causes an inhibi-
tion, apparently by a reflex effect upon the deglutition centre, of the part of
the tract which has not yet entered into contraction, so that the peristaltic
wave does not reach the lower end of the œsophagus until six seconds after
the second act of swallowing.

Nervous Control of Deglutition.—The entire act of swallowing, as has
been said before, is essentially a reflex act. Even the comparatively simple
wave of contraction which sweeps over the œsophagus is apparently due to a
reflex nervous stimulation, and is not a simple conduction of contraction from
one portion of the tube to another. This fact was demonstrated by the
experiments of Mosso,[1] who found that after removal of an entire segment
from the œsophagus the peristaltic wave passed to the portion of the œsoph-
agus left on the stomach side in spite of the anatomical break. The same
experiment was performed successfully on rabbits by Kronecker and Meltzer.
Observation of the stomach end of the œsophagus in this animal showed that
it went into contraction two seconds after the beginning of a swallowing act
whether the œsophagus was intact or ligated or completely divided by a trans-
verse incision. The afferent nerves concerned in this reflex are the sensory
fibres to the mucous membrane of the pharynx and œsophagus, including
branches of the glossopharyngeal, trigeminal, vagus, and superior laryngeal
division of the vagus. Artificial stimulation of this last nerve in the lower
animals is known to produce swallowing movements. Wassilieff[2] records that
in rabbits he was able to produce the swallowing reflex by artificial stimula-
tion of the mucous membrane of the soft palate over a definite area. The

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[1] *Moleschott's Untersuchungen*, 1876, Bd. xi.   [2] *Zeitschrift für Biologie*, 1888, Bd. 24, S. 29.

sensory fibres to this area arise from the trigeminal nerve. The same observer, in experiments upon himself, was unable to locate any particular area of the mucous membrane of the mouth which seemed to be especially connected with the swallowing reflex. The physiological centre of the reflex is supposed to lie quite far forward in the medulla, but its anatomical boundaries have not been satisfactorily defined. It seems probable that in this as in other cases the physiological centre is not a circumscribed collection of nerve-cells, but comprises certain portions, more or less scattered, of the nuclei of origin of the efferent fibres to the muscles of deglutition. These muscles are innervated by fibres from the hypoglossal, facial, trigeminal, glossopharyngeal, and vagus. The latter nerve supplies through some of its branches the entire œsophagus as well as some of the pharyngeal muscles, the muscles closing the glottis, and the aryteno-epiglottidean, which is supposed to aid in depressing the epiglottis.

Movements of the Stomach.

The musculature of the stomach is usually divided into three layers, a longitudinal, an oblique, and a circular coat. The longitudinal coat is continuous at the cardia with the longitudinal fibres of the œsophagus; it spreads out from this point along the length of the stomach, forming a layer of varying thickness; along the curvatures the layer is stronger than on the front and posterior surfaces, while at the pyloric end it increases considerably in thickness, and passes over the pylorus to be continued directly into the longitudinal coat of the duodenum. The layer of oblique fibres is quite incomplete; it seems to be continuous with the circular fibres of the œsophagus and spreads out from the cardia for a certain distance over the front and posterior surfaces of the fundus of the stomach, but toward the pyloric end disappears, seeming to pass into the circular fibres. The circular coat, which is placed between the two preceding layers, is the thickest and most important part of the musculature of the stomach. At the extreme left end of the fundus the circular bands are thin and somewhat loosely placed, but toward the pyloric end they increase much in thickness, forming a strong muscular mass, which, as we shall see, plays the most important part in the movements of the stomach. At the pylorus itself a special development of this layer functions as a sphincter pylori, which with the aid of a circular fold of the mucous membrane makes it possible to shut off the duodenum completely or partially from the cavity of the stomach. The portion of the stomach near the pylorus is frequently designated simply as the "pyloric part," but owing to its distinct structure and functions the more specific name of "antrum pylori" seems preferable. The line of separation between the antrum pylori and the body or fundus of the stomach is made by a special thickening of the circular fibres which forms a structure known as the "transverse band" by the older writers,[1] and described more recently[2] as the "sphincter antri pylorici." This so-called sphincter lies at a distance of seven to ten centimeters from the

[1] See Beaumont: *Physiology of Digestion*, 2d ed., 1847, p. 104.
[2] Hofmeister und Schütz: *Archiv für exper. Pathologie und Pharmakologie*, 1886, Bd. xx.

pylorus. Between it and the pylorus is the "antrum pylori," of which the distinguishing features are the comparative smoothness and paleness of the mucous membrane, the presence of the pyloric as distinguished from the fundic glands, and the existence of a relatively very strong musculature.

The movements of the stomach during digestion have been the subject of much study and experimentation, both in man and the lower animals, but it cannot be said that the mechanism of the movements is as yet completely understood. The fundamental facts to be borne in mind are that during a period of several hours after ordinary food is received into the stomach the musculature of this organ contracts in such a way as to keep the contents in movement, while from time to time the thinner portions of the semi-digested food are sent through the pylorus into the duodenum. There is a certain orderliness in the movement, and especially in the separation and ejection of the more liquid from the solid parts, which indicates that the whole act is well co-ordinated to a definite end. The older physiologists spoke of a selective power of the pylorus in reference to the recurring acts of ejection of the more liquid portions into the intestine, but a phrase of this kind, as applied to a muscular apparatus, is permissible only as a figure of speech, and throws no light whatever upon the nature of the process. It has been the object of recent investigations to discover the mechanical factors involved in these acts and their relations to the musculature known to be present. It has been shown satisfactorily that the movements of the stomach are not dependent upon its connection with the central nervous system. The stomach receives a rich supply of extrinsic nerve-fibres, some of which are distributed to its muscles and serve to regulate its movements, as will be described later; but when these extrinsic nerves are all severed, and indeed when the stomach is completely removed from the body, its movements may still continue in apparently a normal way so long as proper conditions of moisture and temperature are maintained. We must believe, therefore, that the stomach is an automatic organ, using the word automatic in a limited sense to imply essential independence of the central nervous system. The normal stomach at rest is usually quiet, and the stimulus to its movements comes from the presence of the solid or liquid material received into it from the œsophagus. Upon the reception of this material the movements begin, at first feebly but gradually increasing in extent, and continue until most or all of the material has been sent into the duodenum, the length of time required depending upon the nature and amount of the food. The exact character of the movements has been variously described by different observers. Upon man they were carefully studied by Beaumont[1] in his famous observations upon Alexis St. Martin (see p. 225), and the essential points in his description have of late years been confirmed by experiments upon dogs,[2] whose stomachs closely resemble that of man. These

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[1] *The Physiology of Digestion,* 1883.

[2] Hofmeister und Schütz: *Archiv für exper. Pathologie und Pharmakologie,* 1886, Bd. xx.; Moritz: *Zeitschrift für Biologie,* 1895, Bd. xxxii.; Rossbach: *Deutsches Archiv für klinische Medicin,* 1890, Bd. xlvi.

observations all tend to show that the main movements of the stomach are effected by the musculature of the antrum pylori, whose contraction is not only the chief factor in ejecting the material into the duodenum, but also aids in keeping the contents of the stomach in motion. The extent to which contractions occur in the fundic end of the stomach does not seem to be so clearly determined. According to some observers rhythmic movements are absent in the fundus to the left of about the middle of the stomach, this portion simply remaining in a condition of tone; according to others the contractions begin near the œsophageal opening and pass thence toward the pylorus. The very careful experiments of Hofmeister and Schütz upon the isolated stomach of the dog, together with the reliable observations made by Beaumont under such favorable conditions on the human stomach, give us a basis for a description of the sequence and extent of the movements during digestion, which is probably correct in its main features at least, although some of the details still need investigation.

According to these observers a normal movement begins near the cardia by a flattening or constriction which is feeble and is apparent only on the side of the great curvature. This constriction is due to a contraction of the circular muscle-fibres, and the wave thus started passes toward the pylorus, increasing in strength as it goes, while the parts behind previously in contraction slowly relax. This peristaltic wave comes to a stop a short distance in front of the antrum pylori by a constriction involving the whole circumference of the stomach to which Hofmeister and Schütz gave the name of the "pre-antral" constriction; it seems to mark the climax of the peristaltic movement. The obvious effect of this movement so far would be to push forward some of the contents of the fundus into the antrum. Immediately upon the formation of this constriction the strong "sphincter antri pylorici" or transverse band which marks the beginning of the antrum, contracts strongly—so strongly, in fact, in what may be considered normal movements, as to cut off entirely the antrum pylori from the fundus. Following upon this the musculature of the antrum contracts as a whole, squeezing upon its contents and sending them through the narrow opening of the pylorus into the duodenum. If, however, the contents of the antrum are not entirely liquid, but contain some solid particles too large to escape through the narrow pylorus, their presence seems to stimulate an "antiperistaltic" wave in the musculature of the antrum pylori—that is, a muscular wave running in the reverse direction to that of a normal one, from right to left, the effect of which is to throw back these solid particles into the fundus, which is now in communication with the antrum, the sphincter antri pylorici having relaxed. This reversed wave in the antrum seems to have been observed repeatedly by Beaumont upon the human stomach, as well as by Hofmeister and Schütz upon the dog's stomach, and enables us to understand how solid particles thrown against the pylorus are again forced back into the fundus to undergo further digestive and mechanical action. These movements, as a whole, from fundus to pylorus occur with a certain rapidity which varies with the nature and amount of the contents of the stomach and the period of diges-

tion.   In Beaumont's observations the movements of the pylorus are recorded as following each other at intervals of two to three minutes, while upon dogs similar movements are recorded as occurring from three to six times in a minute.

It will be seen that according to this description the movements occur in two phases: first, the feeble peristaltic movement running over the fundus chiefly on the side of the great curvature and resulting in pushing some of the fundic contents into the antrum; second, the sharp contraction of the sphincter antri pylorici followed by a similar contraction of the entire musculature of the antrum, both circular and longitudinal, the effect of which is to squeeze some of the contents into the duodenum.   It is possible that either of these phases, but especially the first, might occur at times without the other, and in the first phase it is probable that the longitudinal fibres of the stomach also contract, shortening the organ in its long diameter and aiding in the propulsive movement, but actual observation of this factor has not been successfully made.   It can well be understood that a series of these movements occurring at short intervals would result in putting the entire semi-liquid contents of the stomach into constant circulation.   The precise direction of the current set up is not agreed upon, but it is probable that the graphic description given by Beaumont is substantially accurate.   A portion of this description may be quoted, as follows: "The ordinary course and direction of the revolutions of the food are, first, after passing the œsophageal ring, from right to left, along the small arch; thence, through the large curvature, from left to right.   The bolus, as it enters the cardia, turns to the left; passes the aperture; descends into the splenic extremity, and follows the great curvature toward the pyloric end.   It then returns in the course of the small curvature."   The average time taken for one of these complete revolutions, according to observations made by Beaumont, seems to vary from one to three minutes.

It is possible, of course, that this typical circuit taken by the food may often be varied more or less by different conditions, but the muscular movements observed from the outside would seem to be adapted to keeping up a general revolution of the kind described.   The general result upon the food may easily be imagined. It becomes thoroughly mixed with the gastric juice and any liquid which may have been swallowed, and is gradually disintegrated, dissolved, and more or less completely digested so far as the proteid and albuminoid constituents are concerned.   The mixing action is aided, moreover, by the movements of the diaphragm in respiration, since at each descent it presses upon the stomach. The powerful muscular contractions of the antrum serve also to triturate the softened solid particles, and finally the whole mass is reduced to a liquid or semi-liquid condition in which it is known as chyme, and in this condition the rhythmic contractions of the muscles of the antrum eject it into the duodenum. The rhythmic spirting of the contents of the stomach into the duodenum has been noticed by a number of observers by means of duodenal fistulas in dogs, established just beyond the pylorus.   It has been shown also that when the food taken is entirely liquid—water, for example—the stomach is emptied in a

surprisingly short time, within twenty to thirty minutes; if, however, the water is taken with solid food then naturally the time it will remain in the stomach may be much lengthened.

A very interesting part of the mechanism of the stomach the action of which is not thoroughly understood is the sphincter of the pylorus. During the act of digestion this sphincter remains in a condition of tone; whether its tonic contraction is sufficient only to narrow the pylorus, or whether it is sufficient to completely shut off the pylorus so that a partial relaxation must occur with each contraction of the musculature of the antrum, is not sufficiently well known. It has been shown, however, that this part of the circular layer of muscle is distinctly under the control of the extrinsic nerves, its tonicity being increased by impulses received through the vagi and diminished or inhibited by impulses through the splanchnics. It will be seen from the above brief description that the muscles of the antrum pylori do most of the work of the stomach, while in the much larger fundus the food is retained as in a reservoir to be digested and mechanically prepared for expulsion into the intestine, the two parts of the stomach fulfilling therefore somewhat different functions. Moritz[1] has called especial attention to this fact, and points out the great advantage which accrues to the digestive processes in the intestine in having the stomach to retain the bulk of the food swallowed during a meal, while from time to time small portions only are sent into the intestine for more complete digestion and absorption. In this way the intestine is protected from becoming congested, and its digestive and absorptive processes are more perfectly executed.

Extrinsic Nerves to the Muscles of the Stomach.—The stomach receives extrinsic nerve-fibres from two sources; from the two vagi and from the solar plexus. The fibres from the latter source arise ultimately in the spinal cord, pass to some of the thoracic ganglia of the sympathetic system, and thence by way of the splanchnics to the semilunar or solar plexus and then to the stomach. These fibres probably reach the stomach as non-medullated or sympathetic fibres. The vagi where they are distributed to the stomach seem to consist almost entirely of non-medullated fibres also, and probably the fibres distributed to the muscular coat are of this variety. The results of numerous experiments seem to show quite conclusively that in general the fibres received along the vagus path are motor, artificial stimulation of them causing more or less well marked contractions of part or all of the musculature of the stomach. It has been shown that the sphincter pylori as well as the rest of the musculature is supplied by motor fibres from these nerves. The fibres coming through the splanchnics, on the contrary, are mainly inhibitory. When stimulated they cause a dilatation of the contracted stomach and a relaxation of the sphincter pylori. Some observers have reported experiments which seem to show that this anatomical separation of the motor and inhibitory fibres is not complete; that some inhibitory fibres may be found in the vagi and some motor fibres in the splanchnics. The

[1] *Zeitschrift für Biologie*, 1895, Bd. xxxii.

anatomical courses of these fibres are insufficiently known, but there seems to be no question as to the existence of the two physiological varieties. Through their activity, without doubt, the movements of the stomach may be regulated, favorably or unfavorably, by conditions directly or indirectly affecting the central nervous system. Wertheimer[1] has shown experimentally that stimulation of the central end of the sciatic or the vagus nerve may cause reflex inhibition of the tonus of the stomach, and Doyon[2] has confirmed this result in cases where the movements and tonicity of the stomach were first increased by the action of pilocarpin and strychnin. It must be borne in mind, however, that the action of these extrinsic fibres under normal conditions is probably only to regulate the movements of the stomach. As we have seen, even the extirpated stomach under proper conditions seems to execute movements of the normal type. Normally the movements are provoked by a stimulus of some kind, usually the presence of food material in the interior of the stomach. How the stimulus acts in this case, whether directly upon the muscle-fibres or indirectly through the intrinsic ganglia of the stomach, has not been determined, and the evidence for either view is so insufficient that a discussion of the matter at this time would scarcely be profitable. We must wait for more complete investigations upon the physiology as well as the histology of the muscle- and nerve-tissue in this and in other visceral organs constructed on the same type.

MOVEMENTS OF THE INTESTINES.

The muscles of the small and the large intestine are arranged in two layers, an outer longitudinal and an inner circular coat, while between these coats and in the submucous coat there are present the nerve-plexuses of Auerbach and Meissner. The general arrangement of muscles and nerves is similar, therefore, to that prevailing in the stomach, and in accordance with this we find that the physiological activities exhibited are of much the same character, only, perhaps, not quite so complex.

Forms of Movement.—Two main forms of intestinal movement have been distinguished, the peristaltic and the pendular.

Peristalsis.—The peristaltic movement consists in a constriction of the walls of the intestine which beginning at a certain point passes downward away from the stomach, from segment to segment, while the parts behind the advancing zone of constriction gradually relax. The evident effect of such a movement would be to push onward the contents of the intestines in the direction of the movement. It is obvious that the circular layer of muscles is chiefly involved in peristalsis, since constriction can only be produced by contraction of this layer. To what extent the longitudinal muscles enter into the movement is not definitely determined. The term " anti-peristalsis " is used to describe the same form of movement running in the opposite direction—that is, toward the stomach. Anti-peristalsis is usually said not to occur under normal conditions; it has been observed sometimes in isolated pieces of intestine or in the exposed intes-

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[1] *Archives de Physiologie normale et pathologique*, 1892, p. 379.   [2] *Ibid.*, 1895, p. 374.

tine of living animals when stimulated artificially, and Grützner[1] reports a number of curious experiments which seem to show that substances such as hairs, animal charcoal, etc., introduced into the rectum may travel upward to the stomach under certain conditions. The peristaltic wave normally passes downward, and that this direction of movement is dependent upon some definite arrangement in the intestinal walls is beautifully shown by the experiments of Mall[2] and others upon reversal of the intestines. In these experiments a portion of the small intestine was resected, turned round and sutured in place again, so that in this piece what was the lower end became the upper end. In those animals that made a good operative recovery the nutritive condition gradually became very serious, and in the animals killed and examined the autopsy showed accumulation of material at the upper end of the reversed piece of intestine, and great dilatation.

The peristaltic movements of the intestines may be observed upon living animals when the abdomen is opened. If the operation is made in the air and the intestines are exposed to its influence, or if the conditions of temperature and circulation are otherwise disturbed, the movements observed are often violent and irregular. The peristalsis runs rapidly along the intestines and may pass over the whole length in about a minute; at the same time the contraction of the longitudinal muscles gives the bowels a peculiar writhing movement. Movements of this kind are evidently abnormal, and only occur in the body under the strong stimulation of pathological conditions. Normal peristalsis, the object of which is to move the food slowly along the alimentary tract, is quite a different affair. Observers all agree that the wave of contraction is gentle and progresses slowly. It has been studied very successfully, so far as rate of movement is concerned, by experiments upon animals in which a loop of the intestines was resected, to make a "Thiry-Vella" fistula (see p. 246). Cash[3] finds that in such isolated loops foreign substances introduced are propelled at different rates according to the condition of the animal. In the fasting animal it requires from one and a half to two and a half minutes for a distance of one centimeter. During exercise the movement is more rapid, while during the first few hours of digestion, that is the time during which the stomach is emptying its contents into the intestine, the velocity of the movement is greatly increased, requiring only from twenty to fifty seconds to cover a distance of one centimeter. The force of the contraction as measured by Cash in the dog's intestine is very small. A weight of five to eight grams was sufficient to check the onward movement of the substance in the intestine and to set up violent colicky contractions which caused the animal evident uneasiness. We may suppose that under normal conditions each contraction of the antrum pylori of the stomach, which ejects chyme into the duodenum, is followed by a peristalsis that beginning at the duodenum passes slowly downward for a part or all of the small intestine. According to most

[1] *Deutsche medicinische Wochenschrift*, 1894, No. 48.
[2] *The Johns Hopkins Hospital Reports*, vol. i. p. 93.
[3] *Proceedings of the Royal Society*, London, 1887, vol. 41.

observers the movement is blocked at the ileo-cæcal valve, and the peristaltic movements of the large intestine form an independent group similar in all their general characters to those of the small intestine, but weaker and slower.

Mechanism of the Peristaltic Movement.—The means by which the peristaltic movement makes its orderly forward progression have not been satisfactorily determined. The simplest explanation would be to assume that an impulse is conveyed directly from cell to cell in the circular muscular coat, so that a contraction started at any point would spread by direct conduction of the contraction change. This theory, however, does not explain satisfactorily the normal conduction of the wave of contraction always in one direction, nor the fact that a reversed piece of intestine continues to send its waves in what was for it the normal direction. It is possible, therefore, that the co-ordination of the movement may be effected through the local nerve-ganglia, but our knowledge of the mechanism and physiology of these peripheral nerve-plexuses is as yet too incomplete to be applied satisfactorily to the explanation of the movements in question.

Pendular Movements.—In addition to the peristaltic wave a second kind of movement may be observed in the exposed intestines of a living animal. This movement is characterized by a gentle swinging to and fro of the different loops, whence its name of pendular movement. The oscillations occur at regular intervals, and are usually ascribed to rhythmic contractions of the longitudinal muscles. Mall,[1] however, believes that the main feature of this movement is a rhythmic contraction of the circular muscles, involving a part or all of the intestines. He prefers to speak of the movements as rhythmic instead of pendular contractions, and points out that owing to the arrangement of the blood-vessels in the coats of the intestine the rhythmic contractions should act as a pump to expel the blood from the submucous venous plexus into the radicles of the superior mesenteric vein, and thus materially aid in keeping up the circulation through the intestine and in maintaining a good pressure in the portal vein, in much the same way as happens in the case of the spleen (see p. 272). How far these rhythmic or pendular contractions occur under perfectly normal conditions has not been determined.

Extrinsic Nerves of the Intestines.—As in the case of the stomach, the small intestine and the greater part of the large intestine receive viscero-motor nerve-fibres from the vagi and the sympathetic chain. The former, according to most observers, when artificially stimulated cause movements of the intestine, and are therefore regarded as the motor fibres. It seems probable, however, that the vagi carry or may carry in some animals inhibitory fibres as well, and that the motor effects usually obtained upon stimulation are due to the fact that in these nerves the motor fibres predominate. The fibres received from the sympathetic chain, on the other hand, give mainly an inhibitory effect when stimulated, although some motor fibres apparently may take this path. Bechterew and Mislawski[2] state that the sympathetic fibres for the small intestine emerge from

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[1] *The Johns Hopkins Hospital Reports*, vol. i. p. 37.
[2] *Du Bois-Reymond's Archiv für Physiologie*, 1889, Suppl. Bd.

the spinal cord as medullated fibres in the sixth dorsal to the first lumbar spinal nerves, and pass to the sympathetic chain in the splanchnic nerves and thence to the semilunar plexus, while the sympathetic fibres to the large intestine and rectum arise in the four lower lumbar and the three upper sacral spinal nerves. According to Langley and Anderson[1] the descending colon and rectum receive a double nerve-supply—first from the lumbar spinal nerves (second to fifth), the fibres passing through the sympathetic ganglia and the inferior mesenteric plexus and causing chiefly an inhibition ; second, through the sacral nerves, the fibres passing through the nervus erigens and the hypogastric plexus and causing chiefly contraction of the circular muscle.

These extrinsic fibres undoubtedly serve for the regulation of the movements of the bowels from the central nervous system ; conditions which influence the central system, either directly or indirectly, may thus affect the intestinal movements. The paths of these fibres through the central nervous system are not known, but there are evidently connections extending to the higher brain-centres, since psychical states are known to influence the movements of the intestine, and according to some observers stimulation of portions of the cerebral cortex may produce movements or relaxation of the walls of the small and large intestines. As in the case of the stomach, the extrinsic fibres seem to have only a regulatory influence. When they are completely severed the tonicity of the walls of the intestine is not altered, and peristaltic and rhythmic movements may still occur. The same results may be obtained even upon excised portions of the intestines (Salvioli, Mall). It seems probable, therefore, that normal peristalsis in the living animal may be effected independently of the central nervous system, although its character and strength is subject to regulation through the medium of the viscero-motor fibres, in much the same way, and possibly to as great an extent, as the movements of the heart are controlled through its extrinsic nerves.

Effect of Various Conditions upon the Intestinal Movements.—Experiments have shown that the movements of the intestines may be evoked in many ways beside direct stimulation of the extrinsic nerves. Chemical stimuli may be applied directly to the intestinal wall. The most noteworthy reaction of this kind is the curious effect of potassium and sodium salts as first described by Nothnagel.[2] Potassium salts in proper concentration excite a strong local contraction of the circular fibres, producing a deep constriction at the point of application of the stimulus. Sodium salts, on the contrary, produce a contraction above the point of application which subsequently spreads for some distance, apparently in the direction of a normal persistalsis, since its effect is to force the contents downward. Violent movements may be produced also by shutting off the blood-supply, and again temporarily when the supply is re-established. A condition of dyspnœa may also start movements in the intestines or in some cases inhibit movements which are already in progress, the stimulus in this case seeming to act upon the central nervous system and to stimulate both the motor

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[1] *Journal of Physiology*, 1895, vol. xviii. p. 67.
[2] *Virchow's Archiv für pathologische Anatomie und Physiologie*, 1882, Bd. 88, S. 1.

and the inhibitory fibres. Oxygen gas within the bowels tends to suspend the movements of the intestine, while CO_2, CH_4, and H_2S act as stimuli, increasing the movements. Organic acids, such as acetic, propionic, formic, and caprylic, which may be formed normally within the intestine as the result of bacterial action, act also as strong stimulants.[1]

Defecation.—The undigested and indigestible parts of the food, together with some of the débris and secretions from the alimentary tract, are carried slowly through the large intestine by its peristaltic movements and eventually reach the sigmoid flexure and rectum. Here the nearly solid material stimulates by its pressure the sensory nerves of the rectum and produces a distinct sensation and desire to defecate. The fecal material is retained within the rectum by the action of the two sphincter muscles which close the anal opening. One of these muscles, the internal sphincter, is a strong band of the circular layer of involuntary muscles which forms one of the coats of the rectum. When the rectum contains fecal material this muscle seems to be thrown into a condition of tonic contraction until the act of defecation begins, when it is relaxed. The sphincter is composed of involuntary muscle and is innervated by fibres arising partly from the sympathetic system, and in part through the nervus erigens, from the sacral spinal nerves. The external sphincter ani is composed of striated muscle-tissue and is under the control of the will to a certain extent; when, however, the stimulus from the rectum is sufficiently intense, voluntary control is overcome and this sphincter is also relaxed. The act of defecation is in part voluntary and in part involuntary. The involuntary factor is found in the contractions of the strongly developed musculature of the rectum, especially the circular layer, which serves to force the feces onward, and the relaxation of the internal sphincter. It seems that these two acts are mainly caused by reflex stimulation from the lumbar spinal cord, although it is probable that the rectum, like the rest of the alimentary tract, is capable of automatic contractions. The rectal muscles receive a double nervous supply, containing physiologically both motor and inhibitory fibres. Some of these fibres come from the nervus erigens by way of the hypogastric plexus, and some arise from the lumbar cord and pass through the corresponding sympathetic ganglia, inferior mesenteric ganglion, and hypogastric nerve. It has been asserted that stimulation of the nervus erigens causes contraction of the longitudinal muscles and inhibition of the circular muscles, while stimulation of the hypogastric nerve causes contraction of the circular muscles and inhibition of the longitudinal layer. This division of activity is not confirmed by the recent experiments of Langley and Anderson.[2]

The voluntary factor in defecation consists in the inhibition of the external sphincter and the contraction of the abdominal muscles. When these latter muscles are contracted and at the same time the diaphragm is prevented from moving upward by the closure of the glottis, the increased abdominal pressure is brought to bear upon the abdominal and pelvic viscera, and aids strongly in pressing the contents of the descending colon and sigmoid flexure into the

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[1] Bokai: *Archiv für exper. Pathologie und Pharmakologie*, 1888, Bd. 24, S. 153.   [2] *Op. cit.*

rectum. The pressure in the abdominal cavity is still further increased if a deep inspiration is first made and then maintained during the contraction of the abdominal muscles. Although the act of defecation is normally initiated by voluntary effort, it may also be aroused by a purely involuntary reflex when the sensory stimulus is sufficiently strong. Goltz [1] has shown that in dogs in which the spinal cord had been severed in the lower thoracic region defecation was performed normally, the external sphincter being relaxed.

It would seem that the whole act of defecation is at bottom an involuntary reflex. The physiological centre for the movement lies in the lumbar cord, and has sensory and motor connections with the rectum and the muscles of defecation, but this centre is in part at least provided with connections with the centres of the cerebrum through which the act may be controlled by voluntary impulses and by various psychical states, the effect of emotions upon defecation being a matter of common knowledge. In infants the essentially involuntary character of the act is well seen.

Vomiting.—The act of vomiting causes an ejection of the contents of the stomach through the œsophagus and mouth to the exterior. It was long debated whether the force producing this ejection comes from a strong contraction of the walls of the stomach itself or whether it is due mainly to the action of the walls of the abdomen. A forcible spasmodic contraction of the abdominal muscles takes place, as may easily be observed by any one upon himself, and it is now believed that the contraction of these muscles is the principal factor in vomiting. Magendie found that if the stomach was extirpated and a bladder containing water was substituted in its place and connected with the œsophagus, injection of an emetic caused a typical vomiting movement with ejection of the contents of the bladder. Gianuzzi showed, on the other hand, that upon a curarized animal vomiting could not be produced by an emetic —because, apparently, the muscles of the abdomen were paralyzed by the curare. There are on record, however, a number of observations which tend to show that the stomach is not entirely passive during the act. On the contrary, it may exhibit contractions, more or less violent in character, which while insufficient in themselves to eject its contents, probably aid in a normal act of vomiting. The act of vomiting is in fact a complex reflex movement into which many muscles enter. The following events are described : The vomiting is usually preceded by a sensation of nausea and a reflex flow of saliva into the mouth. These phenomena are succeeded or accompanied by retching movements, which consist essentially in deep spasmodic inspirations with a closed glottis. The effect of these movements is to compress the stomach by the descent of the diaphragm, and at the same time to increase decidedly the negative pressure in the thorax, and therefore in the thoracic portion of the œsophagus. During one of these retching movements the act of vomiting is effected by a convulsive contraction of the abdominal wall which exerts a sudden additional strong pressure upon the stomach. At the same time the cardiac orifice of the stomach is dilated, possibly by an inhibition of the sphincter, aided it is sup-

[1] *Archiv für die gesammte Physiologie*, 1874, Bd. viii. S. 460.

posed by the contraction of the longitudinal muscle-fibres of the œsophagus and the oblique fibres of the muscular coat of the stomach. The stomach contents are, therefore, forced violently out of the stomach through the œsophagus, the negative pressure in the latter probably assisting in the act. The passage through the œsophagus is effected mainly by the force of the contraction of the abdominal muscles; there is no evidence of antiperistaltic movements on the part of the œsophagus itself. During the ejection of the contents of the stomach the glottis is kept closed by the adductor muscles, and usually the nasal chamber is likewise shut off from the pharynx by the contraction of the posterior pillars of the fauces on the palate and uvula. In violent vomiting, however, the vomited material may break through this latter barrier and be ejected partially through the nose.

Nervous Mechanism of Vomiting.—That vomiting is a reflex act is abundantly shown by the frequency with which it is produced in consequence of the stimulation of sensory nerves or as the result of injuries to various parts of the central nervous system. After lesions or injuries of the brain vomiting often results. Disagreeable emotions and disturbances of the sense of equilibrium may produce the same result. Irritation of the mucous membrane of various parts of the alimentary canal (as, for example, tickling the back of the pharynx with the finger), disturbances of the urogenital apparatus, artificial stimulation of the trunk of the vagus and of other sensory nerves, may all cause vomiting. Under ordinary conditions, however, irritation of the sensory nerves of the gastric mucous membrane is the most common cause of vomiting. This effect may result from the products of fermentation in the stomach in cases of indigestion, or may be produced intentionally by local emetics, such as mustard, taken into the stomach. The afferent path in this case is through the sensory fibres of the vagus. The efferent paths of the reflex are found in the motor nerves innervating the muscles concerned in the vomiting, namely, the vagus, the phrenics, and the spinal nerves supplying the abdominal muscles. Whether or not there is a definite vomiting centre in which the afferent impulses are received and through which a co-ordinated series of efferent impulses is sent out to the various muscles, has not been satisfactorily determined. It has been shown that the portion of the nervous system through which the reflex is effected lies in the medulla. But it has been pointed out that the muscles concerned in the act are respiratory muscles. Vomiting in fact consists essentially in a simultaneous spasmodic contraction of expiratory (abdominal) muscles and inspiratory muscles (diaphragm). It has therefore been suggested that the reflex takes place through the respiratory centre, or some part of it. This view seems to be opposed by the experiments of Thumas,[1] who has shown that when the medulla is divided down the mid-line respiratory movements continue as usual, but vomiting can no longer be produced by the use of emetics. Thumas claims to have located a vomiting centre in the medulla in the immediate neighborhood of the calamus scriptorius. Further evidence, however,

[1] *Virchow's Archiv für pathologische Anatomie*, etc., 1891, Bd. 123, S. 44.

is required upon this point. The act of vomiting may be produced not only as a reflex from various sensory nerves, but may also be caused by direct action upon the medullary centres. The action of apomorphia is most easily explained by supposing that it acts directly on the nerve-centres.

Micturition.—The urine is secreted continuously by the kidneys, is carried to the bladder through the ureters, and is then at intervals finally ejected from the bladder through the urethra by the act of micturition.

Movements of the Ureters.—The ureters possess a muscular coat consisting of an internal longitudinal and external circular layer. The contractions of this muscular coat are the means by which the urine is driven from the pelvis of the kidney into the bladder. The movements of the ureter have been carefully studied by Engelmann.[1] According to his description the musculature of the ureter contracts spontaneously at intervals of ten to twenty seconds (rabbit), the contraction beginning at the kidney and progressing toward the bladder in the form of a peristaltic wave and with a velocity of about twenty to thirty millimeters per second. The result of this movement should be the forcing of the urine into the bladder in a series of gentle rhythmic spirts, and this method of filling the bladder has been observed in the human being. Suter and Mayer[2] report some observations upon a boy in whom there was ectopia of the bladder with exposure of the orifices of the ureters. The flow into the bladder was intermittent and was about equal upon the two sides for the time the child was under observation (three and a half days).

The causation of the contractions of the ureter musculature is not easily explained. Engelmann finds that artificial stimulation of the ureter or of a piece of the ureter may start peristaltic contractions which move in both directions from the point stimulated. He was not able to find ganglion-cells in the upper two-thirds of the ureter, and was led to believe, therefore, that the contraction originates in the muscular tissue independently of extrinsic or intrinsic nerves, and that the contraction wave propagates itself directly from muscle-cell to muscle-cell, the entire musculature behaving as though it were a single, colossal hollow muscle-fibre. The liberation of the stimulus which inaugurates the normal peristalsis of the ureter seems to be connected with the accumulation of urine in its upper or kidney portion. It may be supposed that the urine that collects at this point as it flows from the kidney stimulates the muscular tissue to contraction, either by its pressure or in some other way, and thus leads to an orderly sequence of contraction waves. It is possible, however, that the muscle of the ureter, like that of the heart, is spontaneously contractile under normal conditions, and does not depend upon the stimulation of the urine. Thus, according to Engelmann, section of the ureter near the kidney does not materially affect the nature of the contractions of the stump attached to the kidney, although in this case the pressure of the urine could scarcely act as a stimulus. Moreover, in the case of the rat, in which the ureter is highly contractile, the tube may be cut into several pieces and each piece will continue to

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[1] *Pflüger's Archiv für die gesammte Physiologie*, 1869, Bd. ii. S. 243; Bd. iv. S. 33.

[2] *Archiv für exper. Pathologie und Pharmakologie*, 1893, Bd. 32, S. 241.

exhibit periodic peristaltic contractions. It does not seem possible at present to decide between these two views as to the cause of the contractions. The nature of the contractions, their mode of progression, and the way in which they force the urine through the ureter seem, however, to be clearly established. Efforts to show a regulatory action upon these movements through the central nervous system have so far given only negative results.

Movements of the Bladder.—The bladder contains a muscular coat of plain muscle-tissue, which, according to the usual description, is arranged so as to make an external longitudinal coat and an internal circular or oblique coat. A thin longitudinal layer of muscle-tissue lying to the interior of the circular coat is also described. The separation between the longitudinal and circular layers is not so definite as in the case of the intestine; they seem, in fact, to form a continuous layer, one passing gradually into the other by a change in the direction of the fibres. At the cervix the circular layer is strengthened, and has been supposed to act as a sphincter with regard to the urethral orifice—the so-called sphincter vesicæ internus. Round the urethra just outside the bladder is a circular layer of striated muscle which is frequently designated as the external sphincter or sphincter urethræ. The urine brought into the bladder accumulates within its cavity to a certain limit. It is prevented from escape through the urethra at first by the mere elasticity of the parts at the urethral orifice, aided perhaps by tonic contraction of the internal sphincter, although this function of the circular layer at this point is disputed by some observers. When the accumulation becomes greater the external sphincter is brought into action. If the desire to urinate is strong the external sphincter seems undoubtedly to be controlled by voluntary effort, but whether or not, in moderate filling of the bladder, it is brought into play by an involuntary reflex is not definitely determined. Back-flow of urine from the bladder into the ureters is effectually prevented by the oblique course of the ureters through the wall of the bladder. Owing to this circumstance pressure within the bladder serves to close the mouths of the ureters, and indeed the more completely the higher the pressure. At some point in the filling of the bladder the pressure is sufficient to arouse a conscious sensation of fulness and a desire to micturate. Under normal conditions the act of micturition follows. It consists essentially in a strong contraction of the bladder with a simultaneous relaxation of the external sphincter, if this muscle is in action, the effect of which is to obliterate more or less completely the cavity of the bladder and drive the urine out through the urethra.

The force of this contraction is considerable, as is evidenced by the height to which the urine may spirt from the end of the urethra. According to Mosso the contraction may support, in the dog, a column of liquid two meters high. The contractions of the bladder may be and usually are assisted by contractions of the walls of the abdomen, especially toward the end of the act. As in defecation and vomiting, the contraction of the abdominal muscles, when the glottis is closed so as to keep the diaphragm fixed, serves to increase the pressure in the abdominal and pelvic cavities, and is thus used to assist in or

complete the emptying of the bladder. It is, however, not an essential part of the act of micturition. The last portions of the urine escaping into the urethra are ejected, in the male, in spirts produced by the rhythmic contractions of the bulbo-cavernosus muscle.

Considerable uncertainty and difference of opinion exists as to the physiological mechanism by which this series of muscular contractions, and especially the contractions of the bladder itself, is produced. According to the frequently quoted description given by Goltz[1] the series of events is as follows : The distention of the bladder by the urine causes finally a stimulation of the sensory fibres of the organ and produces a reflex contraction of the bladder musculature which squeezes some urine into the urethra. The first drops, however, that enter the urethra stimulate the sensory nerves there and give rise to a conscious desire to urinate. If no obstacle is presented the bladder then empties itself, assisted perhaps by the contractions of the abdominal muscles. The emptying of the bladder may, however, be prevented, if desirable, by a voluntary contraction of the sphincter urethræ, which opposes the effect of the contraction of the bladder. If the bladder is not too full and the sphincter is kept in action for some time, the contractions of the bladder may cease and the desire to micturate pass off. According to this view the voluntary control of the process is limited to the action of the external sphincter and the abdominal muscles ; the contraction of the bladder itself is purely an unconscious reflex taking place through a lumbar centre.

The experiments of Goltz and others, upon dogs in which the spinal cord was severed at the junction of the lumbar and the thoracic regions, prove that micturition is essentially a reflex act with its centre in the lumbar cord, but a number of physiologists have concluded that the contractions of the bladder itself, in spite of its involuntary musculature, is also under control of the will. Mosso and Pellacani[2] have made experiments upon women which seem to show that this is the case. In these experiments a catheter was introduced into the bladder and connected with a recording apparatus to measure the volume of the bladder. It was found that, in some cases at least, the woman could empty the bladder at will without using the abdominal muscles. The same authors adduce experimental evidence to show that the sensation of fulness and desire to micturate come from sensory stimulation in the bladder itself caused by the pressure of the urine. They point out that the bladder is very sensitive to reflex stimulation ; that every psychical act and every sensory stimulus is apt to cause a contraction or increased tone of the bladder. The bladder is, therefore, subject to continual changes in size from reflex stimulation, and the pressure within it will depend not simply on the quantity of urine but on the condition of tone of the bladder. At a certain pressure the sensory nerves are stimulated and under normal conditions micturition ensues. We may understand, from this point of view, how it happens that we have sometimes a strong desire to micturate when the bladder contains but little

[1] *Pflüger's Archiv für die gesammte Physiologie*, 1874, Bd. viii. S. 478.
[2] *Archives italienne de Biologie*, 1882, tome i.

urine—for example, under emotional excitement. In such cases if the micturition is prevented, probably by the action of the external sphincter, the bladder may subsequently relax and the sensation of fulness and desire to micturate pass away until the urine accumulates in sufficient quantity or the pressure is again raised by some circumstance which causes a reflex contraction of the bladder.

Nervous Mechanism.—According to a recent paper by Langley and Anderson,[1] the bladder in cats, dogs, and rabbits receives motor fibres from two sources: (1) From the lumbar nerves, the fibres passing out in the second to the fifth lumbar nerves and reaching the bladder through the sympathetic chain and the inferior mesenteric ganglion and hypogastric nerves. Stimulation of these nerves causes comparatively feeble contraction of the bladder. (2) From the sacral spinal nerves, the fibres originating in the second and third sacral spinal nerves, or in the rabbit in the third and fourth, and being contained in the so-called nervus erigens. Stimulation of these nerves, or some of them, causes strong contractions of the bladder, sufficient to empty its contents. Little evidence was obtained of the presence of vaso-motor fibres. According to Nawrocki and Skabitschewsky[2] the spinal sensory fibres to the bladder are found in part in the posterior roots of the first, second, third, and fourth sacral spinal nerves, particularly the second and third. When these fibres are stimulated they excite reflexly the motor fibres to the bladder found in the anterior roots of the second and third sacral spinal nerves. Some sensory fibres to the bladder pass by way of the hypogastric nerves. When these are stimulated they produce, according to these authors, a reflex effect upon the motor fibres in the other hypogastric nerve, causing a contraction of the bladder, the reflex occurring through the inferior mesenteric ganglion. This observation has been confirmed by several authorities, and is the best example of a peripheral ganglion serving as a reflex centre. Langley and Anderson,[3] who also obtained this effect, give it a special explanation, contending that it is not a true reflex.

The immediate spinal centre through which the contractions of the bladder may be reflexly stimulated or inhibited lies, according to the experiments of Goltz, in the lumbar portion of the cord, probably between the second and fifth lumbar spinal nerves. In dogs in which this portion of the cord was isolated by a cross section at the junction of the thoracic and lumbar regions, micturition still ensued when the bladder was sufficiently full, and could be called forth reflexly by sensory stimuli, especially by slight irritation of the anal region.

[1] *Journal of Physiology*, 1895, vol. xix. p. 71.
[2] *Pflüger's Archiv für die gesammte Physiologie*, 1891, Bd. 49, S. 141.
[3] *Journal of Physiology*, 1894, vol. xvi. p. 410.

VI. BLOOD AND LYMPH.

BLOOD.

A. General Properties: Physiology of the Corpuscles.

THE blood of the body is contained in a practically closed system of tubes, the *blood-vessels*, within which it is kept circulating by the force of the heart-beat. The blood is usually spoken of as the nutritive liquid of the body, but its functions may be stated more explicitly, although still in quite general terms, by saying that it carries to the tissues food-stuffs after they have been properly prepared by the digestive organs; that it transports to the tissues oxygen absorbed from the air in the lungs; that it carries off from the tissues various waste products formed in the processes of disassimilation, such as urea, uric acid, water, CO_2, etc.; and that in warm-blooded animals it aids in equalizing the temperature of the body. It is quite obvious, from these statements, that a complete consideration of the physiological relations of the blood would involve substantially a treatment of the whole subject of physiology. It is proposed, therefore, in this section to treat the blood in a restricted way—to consider it, in fact, as a tissue in itself, and to study its composition and properties without especial reference to its nutritive relationship to other parts of the body.

Histological Structure.—The blood is composed of a liquid part, the *plasma*, in which float a vast number of microscopic bodies, the *blood-corpuscles*. There are at least three different kinds of corpuscles, known respectively as the *red* corpuscles; the *white* corpuscles or leucocytes, of which in turn there are a number of different kinds; and the *blood-plates*. As the details of structure, size, and number of these corpuscles belong properly to text-books on histology, they will be mentioned only incidentally in this section when treating of the physiological properties of the corpuscles. Blood-plasma, when obtained free from corpuscles, is perfectly colorless in thin layers—for example, in microscopic preparations; when seen in large quantities it shows a slightly yellowish tint, the depth of color varying with different animals. This color is due to the presence in small quantities of a special pigment, the nature of which is not definitely known. The red color of blood is not due, therefore, to coloration of the blood-plasma, but is caused by the mass of red corpuscles held in suspension in this liquid. The proportion by bulk of plasma to corpuscles is usually given, roughly, as two to one.

Blood-serum and Defibrinated Blood.—In connection with the explanation of the term " blood-plasma " just given, it will be convenient to define briefly

the terms "blood-serum" and "defibrinated blood." Blood, after it escapes
from the vessels, usually clots or coagulates; the nature of this process is
discussed in detail on p. 352. The clot, as it forms, gradually shrinks and
squeezes out a clear liquid to which the name *blood-serum* is given. Serum
resembles the plasma of normal blood in general appearance, but differs from
it in composition, as will be explained later. At present we may say, by way
of a preliminary definition, that blood-serum is the liquid part of blood after
coagulation has taken place, as blood-plasma is the liquid part of blood before
coagulation has taken place. If shed blood is whipped vigorously with a rod
or some similar object while it is clotting, the essential part of the clot—
namely, the fibrin—forms differently from what it does when the blood is
allowed to coagulate quietly; it is deposited in shreds on the whipper. Blood
that has been treated in this way is known as *defibrinated blood.* It consists
of blood-serum plus the red and white corpuscles, and as far as appearances
go it resembles exactly normal blood; it has lost, however, the power of clot-
ting. A more complete definition of these terms will be given after the sub-
ject of coagulation has been treated.

Reaction.—The reaction of blood is alkaline, owing mainly to the alka-
line salts, especially the carbonates of soda, dissolved in the plasma. The
degree of alkalinity varies with different animals: reckoned as Na_2CO_3, the
alkalinity of dog's blood corresponds to 0.2 per cent. of this salt; of human
blood, 0.35 per cent. The alkaline reaction of blood is very easily demon-
strated upon clear plasma free from corpuscles, but with normal blood the red
color prevents the direct application of the litmus test. A number of simple
devices have been suggested to overcome this difficulty. For example, the
method employed by Zuntz is to soak a strip of litmus-paper in a concentrated
solution of NaCl, to place on this paper a drop of blood, and, after a few
seconds, to remove the drop with a stream of water or with a piece of filter-
paper. The alkaline reaction becomes rapidly less marked after the blood has
been shed; it varies also slightly under different conditions of normal life
and in certain pathological conditions. After meals, for instance, during the
act of digestion, it is said to be increased, while, on the contrary, exercise
causes a diminution. In no case, however, does the reaction become acid.
For details of the methods used for quantitative determinations of the alka-
linity of human blood, reference must be made to original sources.[1]

Specific Gravity.—The specific gravity of human blood in the adult male
may vary from 1041 to 1067, the average being about 1055. Jones[2] made
a careful study of the variations in specific gravity of human blood under
different conditions of health and disease, making use of a simple method
which requires only a few drops of blood for each determination. He found
that the specific gravity varies with age and sex, that it is diminished after
eating and is increased by exercise, that it falls slowly during the day and
rises gradually during the night, and that it varies greatly in individuals, "so

[1] Peiper: *Virchow's Archiv,* vol. cxvi., 1889, p. 337.
[2] *Journal of Physiology,* vol. xii., 1891, p. 299.

much so that a specific gravity which is normal for one may be a sign of disease in another." The specific gravity of the corpuscles is slightly greater than that of the plasma. For this reason the corpuscles in shed blood, when its coagulation is prevented or retarded, tend to settle to the bottom of the containing utensil, leaving a more or less clear layer of supernatant plasma. Among themselves, also, the corpuscles differ slightly in specific gravity, the red corpuscles being heaviest and the blood-plates being lightest.

Red Corpuscles.—The red corpuscles in man and in all the mammalia, with the exception of the camel and other members of the group Camelidæ, are biconcave circular disks without nuclei; in the Camelidæ they have an elliptical form. Their average diameter in man is given at 7.7μ ($1\mu = 0.001$ of a mm.); their number, which is usually reckoned as so many in a cubic millimeter, varies greatly under different conditions of health and disease. The average number is given as 5,000,000 per cubic mm. for males and 4,500,000 for females. The red color of the corpuscles is due to the presence in them of a pigment known as "hæmoglobin." Owing to the minute size of the corpuscles, their color when seen singly under the microscope is a faint yellowish-red, but when seen in mass they exhibit the well-known blood-red color, which varies from scarlet in arterial blood to purplish-red in venous blood, this variation in color being dependent upon the amount of oxygen contained in the blood in combination with the hæmoglobin. Speaking generally, the function of the red corpuscles is to carry oxygen from the lungs to the tissues. This function is entirely dependent upon the presence of hæmoglobin, which has the power of combining easily with oxygen gas. The physiology of the red corpuscles, therefore, is largely contained in a description of the properties of hæmoglobin.

Condition of the Hæmoglobin in the Corpuscle.—The finer structure of the red corpuscle is not completely known. It is commonly believed that the corpuscle consists of two substances—a delicate, extensible, colorless protoplasmic material, which gives to the corpuscle its shape and which is known as the *stroma*, and the hæmoglobin. The latter constitutes the bulk of the corpuscle, forming as much as 95 per cent. of the solid matter. It was formerly thought that hæmoglobin is disseminated as such in the interstices of the porous spongy stroma, but there seem to be reasons now for believing that it is present in the corpuscles in some combination the nature of which is not fully known. This belief is based upon the fact that Hoppe-Seyler[1] has shown that hæmoglobin while in the corpuscles exhibits certain minor differences in properties as compared with hæmoglobin outside the corpuscles. In various ways the compound of hæmoglobin in the corpuscles may be destroyed, the hæmoglobin being set free and passing into solution in the plasma. Blood in which this change has occurred is altered in color and is known as "laky blood." In thin layers it is transparent, whereas normal blood with the hæmoglobin still in the corpuscles is quite opaque even in very thin strata. Blood may be made laky by the addition of ether, of chloroform, of bile or

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[1] *Zeitschrift für physiologische Chemie*, vol. xiii., 1889, p. 477.

the bile acids, of the serum of other animals, by an excess of water, by alternately freezing and thawing, and by a number of other methods. In connection with two of these methods of discharging hæmoglobin from the corpuscles there have come into use in current medical and physiological literature two technical terms which it may be well to attempt to define.

Globulicidal Action of Serum.—It was shown first by Landois that the serum of one animal may have the property of destroying the red corpuscles in the blood of another animal, thus making the blood laky. This fact, which has since been investigated more fully, is now designated under the term of " globulicidal " action of the serum. It has been found that different kinds of serum show different degrees of globulicidal activity, and that white as well as red corpuscles may be destroyed. Dog's serum or human serum is strongly globulicidal to rabbit's blood. It would seem that this action is not due to mere variations in the amounts of inorganic salts in the different kinds of serum, since the remarkable fact has been discovered that heating serum to 55° or 60° C. for a few minutes destroys its globulicidal action, although such treatment causes no coagulation of the proteids nor any visible change in the liquid. This globulicidal action seems to be associated with a similar destructive effect of serum on bacteria—its so-called " bactericidal action "—but a satisfactory explanation of either phenomenon has not yet been given. The subject is complicated by the fact that the serum of some animals fails to give the globulicidal reaction ; horse's serum, for instance, does not destroy the red corpuscles of rabbit's blood. A discussion of the theories and facts bearing upon the matter would lead too far into pathological literature, to which the reader is referred for further information.

Isotonic Solutions.—When blood or defibrinated blood is diluted with water, a point is soon reached at which hæmoglobin begins to pass out of the corpuscles into the plasma or the serum, and the blood begins to become laky ; to obtain this effect different quantities of water may be required for the blood of different animals, frog's blood, for example, requiring more water than mammalian blood. It appears that the liquid surrounding the corpuscles must have a certain concentration as regards salts or other soluble substances, such as sugar, in order to prevent the entrance of water into the substance of the corpuscle. There exists normally in the red corpuscle a certain quantity of water, determined by the nature of its own substance and the attraction for water exercised by the soluble substances in the liquid surrounding the corpuscle. If the concentration of the outside liquid is diminished, this equilibrium is destroyed and water passes into the corpuscle ; if the dilution has been sufficient, enough water passes into the corpuscle to make it swell and eventually to force out the hæmoglobin. Liquids containing inorganic salts, or other soluble substances with an attraction for water, in quantities sufficient to prevent the imbibition of water by the corpuscles are said to be " isotonic to the corpuscles." Red corpuscles suspended in such liquids do not change in shape nor lose their hæmoglobin. When solutions of different substances are compared from this standpoint, it is found that the concentration necessary varies with

the substance used. Thus, a solution of NaCl of 0.64 per cent. is isotonic with a solution of sugar of 5.5 per cent. or a solution of KNO_3 of 1.09 per cent. When placed in any of these three solutions red corpuscles do not take up water—at least not in quantities sufficient to discharge the hæmoglobin. For a more complete account of these relations the reader is referred to original sources (Hamburger[1]). It may be said that the term was introduced first in connection with plant-cells. In the animal body it happens that the isotonic relations of certain substances have been worked out for the red corpuscles, but similar relations must exist with reference to the other cells. Speaking generally, it may be said that the composition of normal blood and lymph is isotonic to the tissue-elements, and that it must be kept so to preserve the cells from injury.

Nature and Amount of Hæmoglobin.—Hæmoglobin is a very complex substance belonging to the group of combined proteids. (For the definition and classification of proteids, as well as for the purely chemical properties of hæmoglobin and its derivatives, reference must be made to the section on " The Chemistry of the Body.") When decomposed in various ways hæmoglobin breaks up into a proteid (globulin, 96 per cent.) and a simpler pigment (hæmatin, 4 per cent.). When the decomposition takes place in the absence of oxygen, the products formed are globulin and hæmochromogen, and the decomposition seems to be of the nature of a simple dissociation. Hæmochromogen in the presence of oxygen quickly undergoes oxidation to the more stable hæmatin. Hoppe-Seyler has shown that hæmochromogen possesses the chemical grouping which gives to hæmoglobin its power of combining readily with oxygen and its distinctive absorption spectrum. On the basis of facts such as these, hæmoglobin may be defined as a compound of a proteid body with hæmochromogen. It seems, then, that although the hæmochromogen portion is the essential thing, giving to the molecule of hæmoglobin its valuable physiological properties as a respiratory pigment, yet in the blood-corpuscles this substance is incorporated into a much larger and more unstable molecule, whose behavior toward oxygen is different from that of the hæmochromogen itself, the difference being mainly in the fact that the hæmoglobin as it exists in the corpuscles forms with oxygen a comparatively feeble combination which may be broken up readily with liberation of the gas.

Hæmoglobin is widely distributed throughout the animal kingdom, being found in the blood-corpuscles of mammalia, birds, reptiles, amphibia, and fishes, and in the blood or blood-corpuscles of many of the invertebrates. The composition of its molecule is found to vary somewhat in different animals, so that, strictly speaking, there are probably a number of different forms of hæmoglobin—all, however, closely related in chemical and physiological properties. Elementary analysis of dog's hæmoglobin shows the following percentage composition (Jaquet): C 53.91; H 6.62, N 15.98, S 0.542, Fe 0.333, O 22.62. Its molecular formula is given as $C_{758}H_{1203}N_{195}S_3FeO_{218}$, which would make the molecular weight 16,669. Other estimates are given of the molecular formula, but they agree at least in showing that the molecule

[1] Du Bois-Reymond's *Archiv für Physiologie*, 1886, p. 476; 1887, p. 31.

is of enormous size. The molecular formula for hæmochromogen is much simpler; it is usually given as $C_{34}H_{36}N_4FeO_5$. The exact amount of hæmoglobin in human blood varies naturally with the individual and with different conditions of life. According to Preyer,[1] the average amount for the adult male is 14 grams of hæmoglobin to each 100 grams of blood. It is estimated that in the blood of a man weighing 68 kilos. there are contained about 750 grams of hæmoglobin, which is distributed among some twenty-five trillions of corpuscles, giving a total superficial area of about 3200 square meters. Practically all of this large surface of hæmoglobin is available for the absorption of oxygen from the air in the lungs, for, owing to the great number and the minute size of the capillaries, the blood, in passing through a capillary area, becomes subdivided to such an extent that the red corpuscles stream through the capillaries, one may say, in single file. In circulating through the lungs, therefore, each corpuscle becomes exposed more or less completely to the action of the air, and the utilization of the entire quantity of hæmoglobin must be nearly perfect. It may be worth while to call attention to the fact that the biconcave form of the red corpuscle increases the superficies of the corpuscle and tends to make the surface exposure of the hæmoglobin more complete.

Compounds with Oxygen and other Gases.—Hæmoglobin has the property of uniting with oxygen gas in certain definite proportions, forming a true chemical compound. This compound is known as *oxyhæmoglobin;* it is formed whenever blood or hæmoglobin solutions are exposed to air or otherwise brought into contact with oxygen. Each molecule of hæmoglobin is supposed to combine with one molecule of oxygen, and it is usually estimated that 1 gram of dried hæmoglobin (dog) can take up 1.59 c.c. of oxygen measured at 0° C. and 760 mm. of barometric pressure. Oxyhæmoglobin is not a very firm compound. If placed in an atmosphere containing no oxygen, it will be dissociated, giving off free oxygen and leaving behind hæmoglobin, or, as it is often called by way of distinction, "*reduced hæmoglobin.*" This power of combining with oxygen to form a loose chemical compound, which in turn can be dissociated easily when the oxygen-pressure is lowered, makes possible the function of hæmoglobin in the blood as the carrier of oxygen from the lungs to the tissues. The details of this process will be described in the section on Respiration. Hæmoglobin forms with carbon-monoxide gas (CO) a compound, similar to oxyhæmoglobin, which is known as *carbon-monoxide hæmoglobin.* In this compound also the union takes place in the proportion of one molecule of hæmoglobin to one molecule of the gas. The compound formed differs, however, from oxyhæmoglobin in being much more stable, and it is for this reason that the breathing of carbon monoxide gas is liable to prove fatal. The CO unites with the hæmoglobin, forming a firm compound; the tissues of the body are thereby prevented from obtaining their necessary oxygen, and death results from suffocation or asphyxia. Carbon monoxide forms one of the constituents of coal-gas. The well-known fatal effect of breathing coal-gas for some time,

[1] *Die Blutkrystalle*, Jena, 1871.

as in the case of individuals sleeping in a room where gas is escaping, is traceable directly to the carbon monoxide. Nitric oxide (NO) forms also with hæmoglobin a definite compound which is even more stable than the CO-hæmoglobin; if, therefore, this gas were brought into contact with the blood, it would cause death in the same way as the CO.

Oxyhæmoglobin, carbon-monoxide hæmoglobin, and nitric-oxide hæmoglobin are similar compounds. Each is formed, apparently, by a definite combination of the gas with the hæmochromogen portion of the hæmoglobin molecule, and a given weight of hæmoglobin unites presumably with an equal volume of each gas. In marked contrast to these facts, Bohr[1] has shown that hæmoglobin forms a compound with carbon-dioxide gas, *carbo-hœmoglobin*, in which the quantitative relationship of the gas to the hæmoglobin differs from that shown by oxygen. In a mixture of O and CO_2 each gas is absorbed by hæmoglobin solutions independently of the other, so that a solution of hæmoglobin nearly saturated with oxygen can unite with as much CO_2 as though it held no oxygen in combination. Bohr suggests, therefore, that the O and the CO_2 must unite with different portions of the hæmoglobin—the oxygen with the pigment portion, the hæmochromogen, and the CO_2 possibly with the proteid portion. It seems probable that hæmoglobin plays a part in the transportion of the carbon dioxide as well as the oxygen of the blood, but its exact value in this respect as compared with the blood-plasma, which also acts as a carrier of CO_2, has not been definitely determined (see Respiration).

Presence of Iron in the Molecule.—It is probable that iron is quite generally present in the animal tissues in connection with nuclein compounds, but its existence in hæmoglobin is noteworthy because it has long been known and because the important property of combining with oxygen seems to be connected with the presence of this element. According to the analyses made, the proportion of iron in hæmoglobin varies somewhat in different animals: the figures given are from 0.335 to 0.47 per cent. The amount of hæmoglobin in blood may be determined, therefore, by making a quantitative determination of the iron. The amount of oxygen with which hæmoglobin will combine may be expressed by saying that one molecule of oxygen will be fixed for each atom of iron in the hæmoglobin molecule. In the decomposition of hæmoglobin into globulin and hæmatin or globulin and hæmochromogen, which has been spoken of above, the iron is retained in the hæmatin.

Crystals.—Hæmoglobin may be obtained readily in the form of crystals (Fig. 86). As usually prepared, these crystals are really oxyhæmoglobin, but it has been shown that reduced hæmoglobin also crystallizes, although with more difficulty. Hæmoglobin from the blood of different animals varies to a marked degree in respect to the power of crystallization. From the blood of the rat, dog, cat, guinea-pig, and horse, crystals are readily obtained, while hæmoglobin from the blood of man and of most of the vertebrates crystallizes much less easily. Methods for preparing and purifying these crystals will be

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[1] *Skandivavisches Archiv für Physiologie*, 1892, Bd. 3, S. 47.

found in the section on "The Chemistry of the Body." To obtain specimens quickly for examination under the microscope, one of the most certain methods is to take some blood from one of the animals whose hæmoglobin crystallizes

easily, place it in a test-tube, add to it a few drops of ether, shake the tube thoroughly until the blood becomes laky—that is, until the hæmoglobin is discharged into the plasma—and then place the tube on ice until the crystals are deposited. Small portions of the crystalline sediment may then be removed to a glass slide for examination. Hæmoglobin from different animals varies not only as to the ease with which it crystallizes, but in some cases also as to the form that the crystals take. In man and in most of the mammalia hæmoglobin is deposited in the form of rhombic prisms; in the guinea-pig it crystallizes in tetrahedra (*d*, Fig. 86), and in the squirrel in hexagonal plates. The crystals are readily soluble in water, and by repeated crystallizations the hæmoglobin may be obtained perfectly pure. As in the case of other soluble proteid-like bodies, solutions of hæmoglobin are decomposed by alcohol, by mineral acids, by salts of the heavy metals, by boiling,

Fig. 86.—Crystallized hæmoglobin (after Frey): *a, b*, crystals from venous blood of man; *c*, from the blood of a cat; *d*, from the blood of a guinea-pig; *e*, from the blood of a hamster; *f*, from the blood of a squirrel.

etc. Notwithstanding the fact that hæmoglobin crystallizes so readily, it is not easily dialyzable, behaving in this respect like proteids and other colloidal bodies. The compounds which hæmoglobin forms with carbon monoxide (CO) and nitric oxide (NO) are also crystallizable, the crystals being isomorphous with those of oxyhæmoglobin.

Absorption Spectra.—Solutions of hæmoglobin and its derivative compounds, when examined with a spectroscope, give distinctive absorption bands. A brief account of the principle and arrangement of the spectroscope, although unnecessary for those familiar with the elements of Physics, is given by way of introduction to the description of these absorption bands.

Light, when made to pass through a glass prism, is broken up into its constituent rays, giving the play of rainbow colors known as the *spectrum.* A spectroscope is an apparatus for producing and observing a spectrum. A simple form, which illustrates sufficiently well the construction of the apparatus, is shown in Figure 87, P being the glass prism giving the spectrum. Light falls upon this prism through the tube (A) to the left, known as the "collimator tube." A slit at the end of this tube (S) admits a narrow slice of light—lamplight or sunlight—which then, by means of a convex lens at the other end of the tube, is made to fall upon the prism

(P) with its rays parallel. In passing through the prism the rays are dispersed by unequal refraction, giving a spectrum. The spectrum thus produced is examined by the observer with the aid of the telescope (B). When the telescope is properly focussed for the rays entering it from the prism (P), a clear picture of the spectrum is seen. The length of the spectrum will depend upon the nature and the number of prisms through which the light is made to pass. For ordinary purposes a short spectrum is preferable for hæmoglobin bands, and a spectroscope with one prism is generally used. If the source of light is a lamp-flame of some kind, the spectrum is continuous, the colors gradually merging one into another from red to violet. If sunlight is used, the spectrum will be crossed by a number of narrow dark lines known as the "Fraunhofer lines"
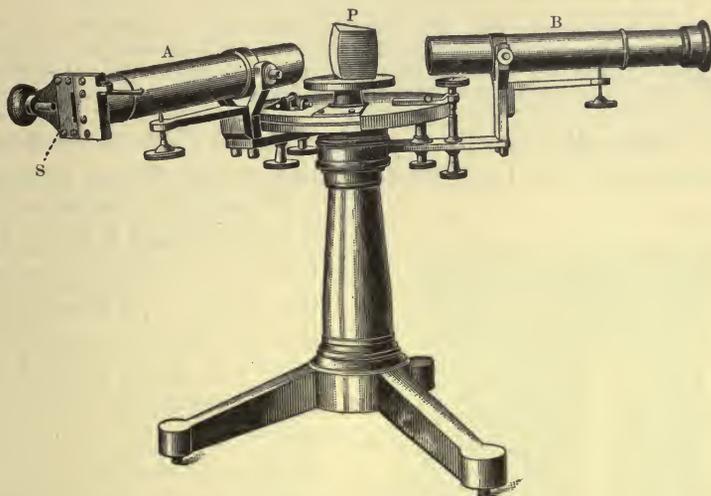
FIG. 87.—Spectroscope: P, the glass prism; A, the collimator tube, showing the slit (s) through which the light is admitted; B, the telescope for observing the spectrum.

(see Pl. I., *Frontispiece*, for an illustration in colors of the solar spectrum). The position of these lines in the solar spectrum is fixed, and the more distinct ones are designated by letters of the alphabet, A, B, C, D, E, etc., as shown in the charts below. If while using solar light or an artificial light a solution of any substance which gives absorption bands is so placed in front of the slit that the light is obliged to traverse it, the spectrum as observed through the telescope will show one or more narrow or broad black bands, which are characteristic of the substance used and which constitute its absorption spectrum. The positions of these bands may be designated by describing their relations to the Fraunhofer lines, or more directly by stating the wave-lengths of the portions of the spectrum between which absorption takes place. Some spectroscopes are provided with a scale of wave-lengths superimposed on the spectrum, and when properly adjusted this scale enables one to read off directly the wave-length of any part of the spectrum.

When very dilute solutions of oxyhæmoglobin are examined with the spectroscope, two absorption bands appear, both occurring in the portion of the spectrum included between the Fraunhofer lines D and E. The band nearer the red end of the spectrum is known as the "α-band;" it is narrower, darker, and more clearly defined than the other, the "β-band" (Fig. 88, and also Pl. I. spectrum 4). With a solution containing 0.09 per cent. of oxyhæmoglobin, and examined in layers one centimeter thick, the α-band extends over the part of the spectrum included between the wave-lengths λ 583

(583 millionths of a millimeter) and λ 571, and the β-band between λ 550 and λ 532 (Gamgee). The width and distinctness of the bands vary naturally with the concentration of the solution used (see Pl. I. spectra 2, 3, 4, and 5),
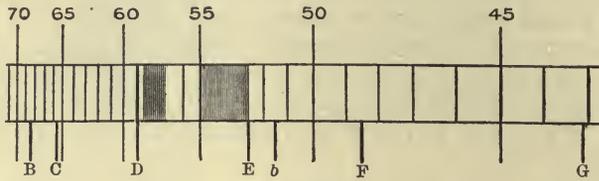
FIG. 88.—Diagrammatic representation of the absorption spectrum of oxyhæmoglobin (after Rollett). The numerals give the wave-lengths in hundred-thousandths of a millimeter; the letters show the positions of the more prominent Fraunhofer lines of the solar spectrum. The red end of the spectrum is to the left. The α-band is to the right of D, the β-band to the left of E.

or, if the concentration remains the same, with the width of the stratum of liquid through which the light passes. With a certain minimal percentage of
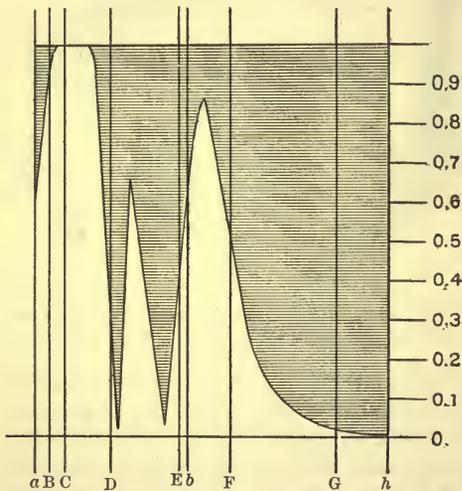
FIG. 89.—Diagram to show the variations in the absorption spectrum of oxyhæmoglobin with varying concentrations of the solution (after Rollett). The numbers to the right give the strength of the oxyhæmoglobin solution in percentages; the letters give the positions of the Fraunhofer lines. To ascertain the amount of absorption for any given concentration up to 1 per cent., draw a horizontal line across the diagram at the level corresponding to the concentration. Where this line passes through the shaded part of the diagram absorption takes place, and the width of the absorption bands is seen at once. The diagram shows clearly that the amount of absorption increases as the solutions become more concentrated, especially the absorption of the blue end of the spectrum. It will be noticed that with concentrations between 0.6 and 0.7 per cent. the two bands between D and E fuse into one.

oxyhæmoglobin (less than 0.01 per cent.) the β-band is lost and the α-band is very faint in layers one centimeter thick. With stronger solutions the bands become darker and wider and finally fuse, while some of the extreme red end and a great deal of the violet end of the spectrum is also absorbed. The variations in the absorption spectrum with differences in concentration are clearly shown in the accompanying illustration from Rollett[1] (Fig. 89); the thickness of the layer of liquid is supposed to be one centimeter. The numbers on the right indicate the percentage strength of the oxyhæmoglobin solutions. It will be noticed that the absorption which takes place as the concentration of the solution increases affects the red-orange end of the spectrum last of all.

Solutions of reduced hæmoglobin examined with the spectroscope show only one absorption band, known sometimes as the "γ-band." This band lies also in the portion of the spectrum included between the lines D and E; its relations to these lines and the bands of oxyhæmoglobin are shown in Figure 90 and in Pl. I. spectrum 6. The

[1] Hermann's *Handbuch der Physiologie*, vol. iv., 1880.

γ-band is much more diffuse than the oxyhæmoglobin bands, and its limits therefore, especially in weak solutions, are not well defined; in solutions of blood diluted 100 times with water, which would give a hæmoglobin solution of about 0.14 per cent., the absorption band lies in the part of the spectrum included between the wave-lengths λ 572 and λ 542. The width
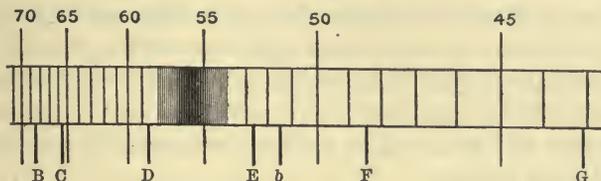
FIG. 90.—Diagrammatic representation of the absorption spectrum of hæmoglobin (reduced hæmoglobin) (after Rollett). The numerals give the wave-lengths in hundred-thousandths of a millimeter; the letters show the positions of the more prominent Fraunhofer lines of the solar spectrum. The red end of the spectrum is to the left. The single diffuse absorption band lies between D and E.

and distinctness of this band vary also with the concentration of the solution. This variation is sufficiently well shown in the accompanying illustration (Fig. 91), which is a companion figure to the one just given for oxyhæmoglobin Fig. 89). It will be noticed that the last light to be absorbed in this case is partly in the red end and partly in the blue, thus explaining the purplish color of hæmoglobin solutions and of venous blood. Oxyhæmoglobin solutions can be converted to hæmoglobin solutions, with a corresponding change in the spectrum bands, by placing the former in a vacuum or, more conveniently, by adding reducing solutions. The solutions most commonly used for this purpose are ammonium sulphide and Stokes's reagent.[1] If a solution of reduced hæmoglobin is shaken with air, it quickly changes to oxyhæmoglobin and gives two bands instead of one when examined through the spectroscope. Any given solution may be changed in this way from oxyhæmoglobin to hæmoglobin, and the reverse, a great number of times,·thus demonstrating the facility with which hæmoglobin takes up and surrenders oxygen.
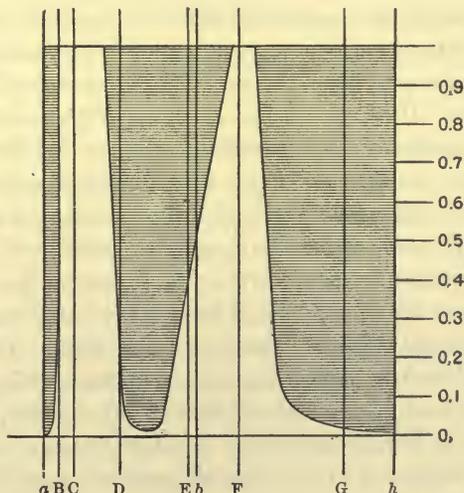
FIG. 91.—Diagram to show the variations in the absorption spectrum of reduced hæmoglobin with varying concentrations of the solution (after Rollett). The numbers to the right give the strength of the hæmoglobin solution in percentages; the letters give the positions of the Fraunhofer lines. For further directions as to the use of the diagram, see the description of Figure 89.

[1] Stokes's reagent is an ammoniacal solution of a ferrous salt. It is made by dissolving 2 parts (by weight) of ferrous sulphate, adding 3 parts of tartaric acid, and then ammonia to distinct alkaline reaction. A permanent precipitate should not be obtained.

Solutions of carbon-monoxide hæmoglobin also give a spectrum with two absorption bands closely resembling in position and appearance those of oxy-hæmoglobin (see Pl. I. spectrum 7). They are distinguished from the oxy-hæmoglobin bands by being slightly nearer the blue end of the spectrum, as may be demonstrated by observing the wave-lengths or, more conveniently, by superimposing the two spectra. Moreover, solutions of carbon-monoxide hæmoglobin are not reduced to hæmoglobin by adding Stokes's liquid, two bands being still seen after such treatment. A solution of carbon-monoxide hæmoglobin suitable for spectroscopic examination may be prepared easily by passing ordinary coal-gas through a dilute oxyhæmoglobin solution for a few minutes and then filtering.

Derivative Compounds of Hæmoglobin.—A number of compounds directly related to hæmoglobin have been described, some of them being found normally in the body. Brief mention is made of the best known of these substances, but for the details of their preparation and chemical proper-ties reference must be made to the section on "The Chemistry of the Body."

Methæmoglobin is a compound obtained by the action of oxidizing agents on hæmoglobin; it is frequently found, therefore, in blood stains or patho-logical liquids containing blood which have been exposed to the air for some time. It is now supposed to be identical in composition with oxyhæmoglobin, with the exception that the oxygen is held in more stable combination. Methæmoglobin crystallizes in the same form as oxyhæmoglobin, and has a characteristic spectrum (Pl. I. spectrum 8).

Hæmochromogen ($C_{34}H_{36}N_4FeO_5$) is the substance obtained when hæmo-globin is decomposed by acids or by alkalies in the absence of oxygen. It crystallizes and has a characteristic spectrum.

Hæmatin ($C_{32}H_{32}N_4FeO_4$) is obtained when oxyhæmoglobin is decomposed by acids or by alkalies in the presence of oxygen. It is amorphous and has a characteristic spectrum (Pl. I. spectra 9 and 10).

Hæmin ($C_{32}H_{30}N_4FeO_3HCl$) is a compound of hæmatin and HCl, and is readily obtained in crystalline form. It is much used in the detection of blood in medico-legal cases, as the crystals are very characteristic and are easily obtained from blood-clots or blood-stains, no matter how old these may be.

Hæmatoporphyrin ($C_{32}H_{36}N_4O_6$) is a compound characterized by the absence of iron. It is frequently spoken of as "iron-free hæmatin." It is obtained by the action of strong sulphuric acid on hæmatin.

Hæmatoidin ($C_{16}H_{18}N_2O_3$) is the name given to a crystalline substance found in old blood-clots, and formed undoubtedly from the hæmoglobin of the clotted blood. It has been shown to be identical with one of the bile-pigments, bilirubin. Its occurrence is interesting in that it demonstrates the relationship between hæmoglobin and the bile-pigments.

Histohæmatins are a group of pigments said to be present in many of the tissues—for example, the muscles. They are supposed to be respiratory pig-ments, and are related physiologically, and possibly chemically, to hæmoglobin. They have not been isolated, but their spectra have been described.

Bile-pigments and Urinary Pigments—Hæmoglobin is regarded as the parent-substance of the bile-pigments and the urinary pigments.

Origin and Fate of the Red Corpuscles.—The mammalian red corpuscle is a cell that has lost its nucleus. It is not probable, therefore, that any given corpuscle lives for a great while in the circulation. This is made more certain by the fact that hæmoglobin is the mother-substance from which the bile-pigments are made, and, as these pigments are being excreted continually, it is fair to suppose that red corpuscles are as steadily undergoing disintegration in the blood-stream. Just how long is the average life of the corpuscles has not been determined, nor is it certain where and how they go to pieces. It has been suggested that their destruction takes place in the spleen, but the observations advanced in support of this hypothesis are not very numerous or conclusive. Among the reasons given for assuming that the spleen is especially concerned in the destruction of red corpuscles, the most weighty is the histological fact that one can sometimes find in teased preparations of spleen-tissue certain large cells which contain red corpuscles in their cell-substance in various stages of disintegration. It has been supposed that the large cells actually ingest the red corpuscles, selecting those, presumably, which are in a state of physiological decline. Against this idea a number of objections may be raised. Large leucocytes with red corpuscles in their interior are not found so frequently nor so constantly in the spleen as we would expect should be the case if the act of ingestion were constantly going on. There is some reason for believing, indeed, that the whole act of ingestion may be a post-mortem phenomenon; that is, after the cessation of the blood-stream the amœboid movements of the large leucocytes continue, while the red corpuscles lie at rest—conditions which are favorable to the act of ingestion. It may be added also that the blood of the splenic vein contains no hæmoglobin in solution, indicating that no considerable dissolution of red corpuscles is taking place in the spleen. Moreover, complete extirpation of the spleen does not seem to lessen materially the normal destruction of red corpuscles, if we may measure the extent of that normal destruction by the quantity of bile-pigment formed in the liver, remembering that hæmoglobin is the mother-substance from which the bile-pigments are derived. It is more probable that there is no special organ or tissue charged with the function of destroying red corpuscles, and that they undergo disintegration and dissolution while in the blood-stream and in any part of the circulation, the liberated hæmoglobin being carried to the liver and excreted in part as bile-pigment. The continual destruction of red corpuscles implies, of course, a continual formation of new ones. It has been shown satisfactorily that in the adult the organ for the reproduction of red corpuscles is the red marrow of bones. In this tissue *hæmatopoiesis*, as the process of formation of red corpuscles is termed, goes on continually, the process being much increased after hemorrhages and in certain pathological conditions. The details of the histological changes will be found in the text-books of histology. It is sufficient here to state simply that a group of nucleated colorless cells, erythroblasts, is found in the red marrow.

These cells multiply by karyokinesis, and the daughter-cells eventually produce hæmoglobin in their cytoplasm, thus forming nucleated red corpuscles. The nuclei are subsequently lost, either by disintegration or, more likely, by extrusion, and the newly-formed non-nucleated red corpuscles are forced into the blood-stream, owing to a gradual change in their position during development caused by the growing hæmatopoietic tissue. When the process has been greatly accelerated, as after severe hemorrhages or in certain pathological conditions, red corpuscles still retaining their nuclei may be found in the circulating blood, having been forced out prematurely as it were. Such corpuscles may subsequently lose their nuclei while in the blood-stream. In the embryo, hæmatopoietic tissue is found in parts of the body other than the marrow, notably in the liver and spleen, which at that time serve as organs for the production of new red corpuscles. In the blood of the young embryo nucleated red corpuscles are at first abundant, but they become less numerous as the fetus grows older.[1]

Variations in the Number of Red Corpuscles.—The average number of red corpuscles for the adult male, as has been stated already, is usually given as 5,000,000 per cubic mm. The number is found to vary greatly, however. Outside of pathological conditions, in which the diminution in number may be extreme, differences have been observed in human beings under such conditions as the following: The number is less in females (4,500,000); it varies in individuals with the constitution, nutrition, and manner of life; it varies with age, being greatest in the fetus and in the new-born child; it varies with the time of the day, showing a distinct diminution after meals; in the female it varies somewhat in menstruation and in pregnancy, being slightly increased in the former and diminished in the latter condition. Perhaps the most interesting example of variation in the number of red corpuscles is that which occurs with changes in altitude. Residence in high altitudes is quickly followed by a marked increase in the number of red corpuscles. Viault[2] has recently shown that living in the mountains two weeks at an altitude of 4392 meters caused an increase in the corpuscles from 5,000,000 to over 7,000,000 per cubic mm., and in the third week the number reached 8,000,000. From these and similar observations it would seem that a diminished pressure of oxygen in the atmosphere stimulates the hæmatopoietic organs to greater activity, and it is interesting to compare this result with the effect of an actual loss of blood. In the latter case the production of red corpuscles in the red marrow is increased, because, apparently, the anæmic condition causes a diminution in the oxygen-supply to the hæmatopoietic tissue, and thereby stimulates the erythroblastic cells to more rapid multiplication. In the case of a sudden diminution in oxygen-pressure, as happens when the altitude is markedly increased, we may suppose that one result is again a slight diminution in the oxygen-supply to the tissues, including the red marrow, and

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[1] For further details see Howell, "Life History of the Blood-corpuscles," etc., *Journal of Morphology*, vol. iv., 1890.

[2] *La Semaine medicale*, 1890, p. 464.

in consequence the erythroblasts are again stimulated to greater activity. This variation in hæmoglobin with the altitude is an interesting adaptation which ensures always a normal oxygen-capacity for the blood.

Physiology of the Blood-leucocytes.—The function of the blood-leucocytes has been the subject of numerous investigations, particularly in connection with the pathology of blood diseases. Although many hypotheses have been made as the result of this work, it cannot be said that we possess any positive information as to the normal function of these cells in the body. It must be borne in mind in the first place that the blood-leucocytes are not all the same histologically, and it may be that their functions are as diverse as is their morphology. Various classifications have been made, based upon one or another difference in microscopic structure and reaction. Thus, Ehrlich groups the leucocytes according to the size and the staining of the granules contained in the cytoplasm, making in the latter respect three main groups : *oxyphiles* or *eosinophiles*, those whose granules stain only with acid aniline dyes—that is, with dyes in which the acid part of the dye acts as the stain ; *basophiles*, those which stain only with basic dyes ; and *neutrophiles*, those which stain only with neutral dyes[1] (Fig. 92). This classification is frequently used, especially in patholog-
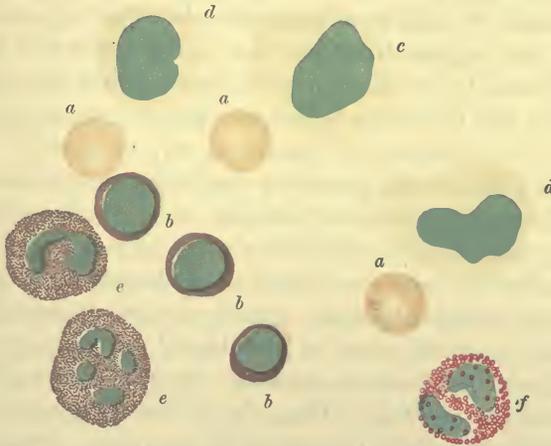
Fig. 92.—Blood stained with Ehrlich's "triple stain" of acid-fuchsin, methyl-green, and orange G. (drawn with the camera lucida from normal blood) (after Osler): *a*, red corpuscles; *b*, lymphocytes; *c*, large mononuclear leucocytes; *d*, transitional forms; *e*, neutrophilic leucocytes with polymorphous nuclei (polynuclear neutrophiles); *f*, eosinophilic leucocytes.

ical literature, but it is not altogether satisfactory, since no definite functional relationship of the granules has been established; and, moreover, it is undecided whether or not the specific granules are permanent or temporary structures in the cells. A safer classification perhaps is the following : 1. *Lymphocytes*, which are small corpuscles with a round vesicular nucleus and very scanty cytoplasm : they are not capable of amœboid movements. These corpuscles are so called because they resemble the leucocytes found in the lymph-gland, and

[1] For a recent discussion and modification of this classification see Kanthack and Hardy, *Journal of Physiology*, vol. xvii., 1894, p. 81.

are supposed in fact to be brought into the blood through the lymph. 2. *Mono-nuclear leucocytes*, which are large corpuscles with a vesicular nucleus and abundant cytoplasm : they have the power of making amœboid movements. 3. *Polymorphous* or *polynucleated leucocytes*, which are large corpuscles with the nucleus divided into lobes that are either entirely separated or are connected by fine protoplasmic threads. This form shows active amœboid movements.

It is impossible to say whether these varieties of blood-leucocytes are distinct histological units which have independent origins and more or less dissimilar functions, or whether, as seems more probable to the writer, they represent different stages in the development of a single type of cell, the lymphocytes forming the youngest and the polymorphic or polynucleated leucocytes the oldest stage. Perhaps the most striking property of the leuco-cytes as a class is their power of making amœboid movements—a charac-teristic which has gained for them the sobriquet of "wandering" cells. By virtue of this property some of them are able to migrate through the walls of blood-capillaries into the surrounding tissues. This process of migration takes place normally, but is vastly accelerated under pathological conditions. As to the function or functions fulfilled by the leucocytes, numerous sugges-tions have been made, some of which may be stated in brief form as follows: (1) They protect the body from pathogenic bacteria. In explanation of this action it has been suggested that they may either ingest the bacteria, and thus destroy them directly, or they may form certain substances, defensive proteids, which destroy the bacteria. Leucocytes that act by ingesting the bacteria are spoken of as "phagocytes" (φαγειν, to eat; κυτος, cell). This theory of their function is usually designated as the "phagocytosis theory of Metschni-koff;" it is founded upon the fact that the amœboid leucocytes are known to ingest foreign particles with which they come in contact. The theory of the protective action of leucocytes has been used largely in pathology to explain immunity from infectious diseases, and for details of experiments in support of it reference must be made to pathological text-books. (2) They aid in the absorption of fats from the intestine. (3) They aid in the absorption of peptones from the intestine. These latter two theories will be spoken of more in detail in describing the process of absorption. (See the section upon Digestion.) It may be noticed here that these theories apply to the leucocytes found so abundantly in the lymphoid tissue of the alimentary canal, rather than to those contained in the blood itself. (4) They take part in the pro-cess of blood-coagulation. A complete statement with reference to this function must be reserved until the phenomenon of coagulation is de-scribed. (5) They help to maintain the normal composition of the blood-plasma as to proteids. It may be said for this view that there is considerable evidence that the leucocytes normally undergo disintegration and dissolu-tion in the circulating blood, to some extent at least. The blood-proteids are peculiar, and they are not obtained directly from the digested food. It is possible that the leucocytes, which are the only typical cells in the blood, aid in keeping up the normal supply of proteids. None of the theories mentioned

has much positive evidence in its favor. It remains possible, on the one hand, that all these as well as other functions may be performed by the leucocytes, and, on the other hand, further discoveries may give an entirely new explanation of the value of these cells to the body. As to the origin of the leucocytes, it is known that they increase in number while in the circulation, undergoing multiplication by karyokinesis; but the greater number are probably produced in the lymph-glands and in the lymphoid tissue of the body, whence they get into the lymph-stream and eventually are brought into the blood.

Physiology of the Blood-plates.—The blood-plates are small circular or elliptical bodies, nearly homogeneous in structure and variable in size (0.5 to 5.5μ), but they are always smaller than the red corpuscles (see Histology). Less is known of their origin, fate, and functions than in the case of the leucocytes. It is certain that they are not independent cells, and it is altogether probable, therefore, that they soon disintegrate and dissolve in the plasma. When removed from the circulating blood they are known to disintegrate very rapidly. This peculiarity, in fact, prevented them from being discovered for a long time after the blood had been studied microscopically. Recent work has shown that they are *formed* elements, and not simply precipitates from the plasma, as was suggested at one time. The theory of Hayem, their real discoverer, that they develop into red corpuscles may also be considered as erroneous. There is considerable evidence to show that in shed blood they take part in the process of coagulation. The nature of this evidence will be described later.

Lilienfeld[1] recently demonstrated that chemically the blood-plates contain a nucleo-albumin (see section on Chemistry of the Body) to which he gives the specific name of "nucleohiston." The same substance is contained in the nuclei of leucocytes. This latter fact may be taken as additional evidence for a view which has already been supported on morphological grounds—that the blood-plates are derived from the nuclei of the leucocytes. According to this theory, when the multinucleated leucocytes go to pieces in the blood the fragments of nuclei contained in them persist for a longer or shorter time as blood-plates, which in time eventually dissolve in the plasma. If this last statement is correct, then it follows that the substance contained in the blood-plates either goes to form one of the normal constituents of the plasma, useful in nutrition or otherwise, or that it forms a waste product which is eliminated from the body. The specific function, if any, of the blood-plates, beyond that of aiding in coagulation, remains to be discovered.

B. Chemical Composition of the Blood; Coagulation; Total Quantity of Blood; Regeneration after Hemorrhage.

Composition of the Plasma and Corpuscles.—Blood (plasma and corpuscles) contains a great variety of substances, as may be inferred from its double relations to the tissues as a source of food-supply and as a means of

[1] *Du Bois-Reymond's Archiv für Physiologie*, 1893, p. 560.

removing the waste products of their functional activity. The constituents existing in quantities sufficiently large for recognition by chemical means are as follows: (1) Water; (2) proteids, of which three varieties at least are known to exist in the plasma—namely, fibrinogen, paraglobulin (serum-globulin), and serum-albumin; (3) combined proteids (hæmoglobin, nucleo-albumins); (4) extractives, including such substances as fats, sugar, urea, lecithin, cholesterin, etc.; and (5) inorganic salts. The proportions of these substances found in the blood of various mammals differ somewhat, although the qualitative composition is practically the same in all.

The following tables, taken from different sources, summarize the main results of the quantitative analyses which have thus far been made:

Analysis of the Whole Blood, Human (C. Schmidt).

	Man (25 years).	Woman (30 years.)
Water	788.71	824.55
Solids	211.29	175.45
Proteids and extractives	191.78	157.93
Fibrin (derived from the fibrinogen)	3.93	1.91
Hæmatin (and iron)	7.70	6.99
Salts	7.88	8.62

Inorganic Salts of Human Blood, 1000 parts (C. Schmidt).

Blood-corpuscles.		Blood-plasma.	
Cl	1.75	Cl	3.536
K_2O	3.091	K_2O	0.314
Na_2O	0.470	Na_2O	3.410
SO_3	0.061	SO_3	0.129
P_2O_5	1.355	P_2O_5	0.145
CaO		CaO	
MgO		MgO	

These acids and bases exist, of course, in the plasma and the corpuscles as salts. It is not possible to determine exactly how they are combined as salts, but Schmidt suggests the following probable combinations:

Probable Salts in the Corpuscles.		Probable Salts in the Plasma.	
Potassium sulphate	0.132	Potassium sulphate	0.281
Potassium chloride	3.679	Potassium chloride	0.359
Potassium phosphate	2.343	Sodium chloride	5.546
Sodium phosphate	0.633	Sodium phosphate	0.271
Sodium carbonate	0.341	Sodium carbonate	1.532
Calcium phosphate	0.094	Calcium phosphate	0.298
Magnesium phosphate	0.060	Magnesium phosphate	0.218

One interesting fact brought out in the above table is the peculiarity in distribution of the potassium and sodium salts between the plasma and the corpuscles. The plasma contains an excess of the total sodium salts, and the corpuscles contain an excess of the potassium salts.

Composition of Blood-plasma (1000 parts).[1]		Composition of Blood-serum (1000 parts).[1]		
	Horse.	Horse.	Man.	Ox.
Water	917.6			
Solids	82.4	85.97	92.07	89.65
Total proteids	69.5	72.57	76.20	74.99
Fibrin (derived from the fibrinogen)	6.5			
Paraglobulin	38.4	45.65	31.04	41.69
Serum-albumin	24.6	26.92	45.16	33.30
Extractives and salts	12.9	13.40	15.88	14.66

Red Corpuscles, Human Blood (Hoppe-Seyler).

	I.	II.	
Oxyhæmoglobin	86.8	94.3	per cent.
Proteid (and nuclein?)	12.2	5.1	"
Lecithin	0.7	0.4	"
Cholesterin	0.3	0.3	"

Leucocytes, Thymus of Calf (Lilienfeld).

In the total dry substance of the corpuscles, which was equal to 11.49 per cent., there was contained—

Proteid	1.76	per cent.
Leuco-nuclein	68.78	"
Histon	8.67	"
Lecithin	7.51	"
Fat	4.02	"
Cholesterin	4.40	"
Glycogen	0.80	"

The extractives present in the blood vary in amount under different conditions. Average estimates of some of them, given in percentages of the entire blood, have been reported as follows:

Dextrose (grape-sugar)	0.117	per cent.
Urea	0.016	"
Lecithin	0.0844	"
Cholesterin	0.041	"

Proteids of the Blood-plasma.—The properties and reactions of proteids and the related compounds, as well as a classification of those occurring in the animal body, are described in the section on the Chemistry of the Body. This description should be read before attempting to study the proteids of the plasma and the part they take in coagulation. Three proteids are usually described as existing in the plasma of circulating blood—namely, fibrinogen, paraglobulin, or, as it is sometimes called, "serum-globulin," and serum-albumin. The first two of these proteids, fibrinogen and paraglobulin, belong to the group of globulins, and hence have many properties in common. Serum-albumin belongs to the group of so-called "native albumins" of which egg-albumin constitutes another member.

Serum-albumin.—This substance is a typical proteid. Its elementary composition, according to Hammarsten, is as follows:

C	H	N	S	O
53.06	6.85	16.04	1.80	22.26

These figures can be regarded as approximate only. Serum-albumin shows the

[1] Hammarsten: *A Text-book of Physiological Chemistry*, 1893 (translated by Mandel).

general reactions of the native albumins. One of its most useful reactions is its behavior toward magnesium sulphate. Serum-albumin usually occurs in liquids together with the globulins, as is the case in blood. If such a liquid is thoroughly saturated with solid $MgSO_4$, the globulins are precipitated completely, while the albumin is not affected. So far as the blood and similar liquids are concerned, a definition of serum-albumin might be given by saying that it comprises all the proteids not precipitated by $MgSO_4$. When its solutions have a neutral or an acid reaction, serum-albumin is precipitated in an insoluble form by heating the solution above a certain degree. Precipitates produced in this way by heating solutions of proteids are spoken of as coagulations—heat coagulations—and the exact temperature at which coagulation occurs is to a certain extent characteristic for each proteid. The temperature of coagulation of serum-albumin is usually given at from 70° to 75° C., but it varies greatly with the conditions. It has been asserted, in fact, that careful heating under proper conditions gives separate coagulations at three different temperatures—namely, 73°, 77°, and 84° C.—indicating the possibility that what is called "serum-albumin" may be a mixture of three or more proteids. Serum-albumin occurs in blood-plasma and blood-serum, in lymph, and in the different normal and pathological exudations found in the body, such as pericardial liquid, hydrocele fluid, etc. The amount of serum-albumin in the blood varies in different animals, ranging among the mammalia from 2.67 per cent. in the horse to 4.52 per cent. in man. In some of the cold-blooded animals it occurs in surprisingly small quantities— 0.36 to 0.69 per cent. As to the source or origin of serum-albumin, it is generally believed that it comes from the digested proteids of the food. It is known that proteid material in the food is not changed at once to serum-albumin during the act of digestion; indeed, it is known that the final product of digestion is a proteid or group of proteids of an entirely different character— namely, peptones and proteoses; but during the act of absorption into the blood these latter bodies are supposed to undergo transformation into serum-albumin. From a physiological standpoint serum-albumin is considered to be the main source of proteid nourishment for the tissues generally. As will be explained in the section on Nutrition, one of the most important requisites in the nutrition of the cells of the body is an adequate supply of proteid material to replace that used up in the chemical changes, the metabolism, of the tissues. Serum-albumin is supposed to furnish a part, at least, of this supply. As long as the serum-albumin is in the blood-vessels it is of course cut off from the tissues. The cells, however, are bathed directly in lymph, and this in turn is formed from the plasma of the blood which is filtered—or, according to some physiologists, secreted—through the vessel-walls. Serum-albumin may be looked upon, then, as a supply of proteid nourishment which is replenished, after every meal containing proteids, by absorption from the alimentary canal.

Paraglobulin, which belongs to the group of globulins, exhibits the general reactions characteristic of the group. As stated above, it is completely precipitated from its solutions by saturation with $MgSO_4$. It is incompletely

precipitated by saturation with common salt (NaCl). In neutral or feebly acid solutions it coagulates upon heating to 75° C. Hammarsten gives its elementary composition as—

C	H	N	S	O
52.71	7.01	15.85	1.11	23.24

These figures must also be received as approximate, as it is not absolutely certain that the substance analyzed was chemically pure. Paraglobulin occurs in blood, in lymph, and in the normal and pathological exudations. The amount of paraglobulin present in blood varies in different animals. Among the mammalia the amount ranges from 1.78 per cent. in rabbits to 4.56 per cent. in the horse. In human blood it is given at 3.10 per cent., being less in amount, therefore, than the serum-albumin. It will be seen, upon examining the tables of composition of the blood-plasma and blood-serum of the horse (p. 349), that more of this proteid is found in the serum than in the plasma. This result, which is usually considered as being true, is explained by supposing that during coagulation some of the leucocytes disintegrate and part of their substance passes into solution as a globulin identical with or closely resembling paraglobulin. The figures given above show that a considerable amount of paraglobulin is normally present in blood. It is reasonable to suppose that, like serum-albumin, this proteid is valuable as a source of nitrogenous food to the tissues. It is uncertain, however, whether it is used by the tissues directly as paraglobulin or is first converted into some other form of proteid. It is entirely unknown, also, whether its value as a proteid supply is in any way different from that of serum-albumin. The origin of paraglobulin remains undetermined. It may arise from the digested proteids absorbed from the alimentary canal, but there is no evidence to support such a view. Another suggestion is that it comes from the disintegration of the leucocytes (and other *formed* elements) of the blood. These bodies are known to contain a small quantity of a globulin resembling paraglobulin, and it is possible that this globulin may be liberated after the dissolution of the leucocytes in the plasma, and thus go to make up the normal supply of paraglobulin. This suggestion, however, is theoretical. The fact remains that at present the origin and the special use of the paraglobulin are entirely unknown.

Fibrinogen is a proteid belonging to the globulin class and exhibiting all the general reactions of this group. It is distinguished from paraglobulin by a number of special reactions; for example, its temperature of heat coagulation is much lower (56° to 60° C.), and it is completely thrown down from its solutions by saturation with NaCl as well as with $MgSO_4$. Its most important and distinctive reaction is, however, that under proper conditions it gives rise to an insoluble proteid, fibrin, whose formation is the essential phenomenon in the coagulation of blood. Fibrinogen has an elementary composition, according to Hammarsten, of—

C	H	N	S	O
52.93	6.90	16.66	1.25	22.26

Fibrinogen is found in blood-plasma, in lymph, and in some cases, though not

always, in the normal and pathological exudations. It is absent from blood-serum, being used up during the process of clotting. It occurs in very small quantities in blood, compared with the other proteids. There is no good method of determining quantitatively the amount of fibrinogen, but estimates of the amount of fibrin, which cannot differ very much from the fibrinogen, show that in human blood it varies from 0.22 to 0.4 per cent. In horse's blood it may be more abundant—0.65 per cent. As to the origin and the special physiological value of this proteid we are, if possible, more in the dark than in the case of paraglobulin, with the exception that fibrinogen is known to be the source of the fibrin of the blood. But clotting is an occasional phenomenon only. What nutritive function, if any, is possessed by fibrinogen under normal conditions is unknown. No satisfactory account has been given of its origin. It has been suggested by different investigators that it may come from the nuclei of disintegrating leucocytes (and blood-plates) or from the dissolution of the extruded nuclei of newly-made red corpuscles, but here again we have only speculations, which cannot be accepted until some experimental proof is advanced to support them.

Coagulation of Blood.—One of the most striking properties of blood is its power of clotting or coagulating shortly after it escapes from the blood-vessels. The general changes in the blood during this process are easily followed. At first shed blood is perfectly fluid, but in a few minutes it becomes viscous and then sets into a soft jelly which quickly becomes firmer, so that the vessel containing it can be inverted without spilling the blood. The clot continues to grow more compact and gradually shrinks in volume, pressing out a smaller or larger quantity of a clear, faintly yellow liquid to which the name *blood-serum* has been given. The essential part of the clot is the fibrin. Fibrin is an insoluble proteid which is absent from normal blood. In shed blood, and under certain conditions in blood while still in the blood-vessels, this fibrin is formed from the soluble fibrinogen. The deposition of the fibrin is peculiar. It is precipitated, if the word may be used, in the form of an exceedingly fine network of delicate threads which permeate the whole mass of the blood and give the clot its jelly-like character. The shrinking of the threads causes the subsequent contraction of the clot. If the blood has not been shaken during the act of clotting, almost all the red corpuscles are caught in the fine fibrin meshwork, and as the clot shrinks these corpuscles are held more firmly, only the clear liquid of the blood being squeezed out, so that it is possible to get specimens of serum containing few or no red corpuscles. The leucocytes, on the contrary, although they are also caught at first in the forming meshwork of fibrin, may readily pass out into the serum in the later stages of clotting, on account of their power of making amœboid movements. If the blood has been agitated during the process of clotting, the delicate network will be broken in places and the serum will be more or less bloody—that is, it will contain numerous red corpuscles. If during the time of clotting the blood is vigorously whipped with a bundle of fine rods, all the fibrin will be deposited as a stringy mass upon the whip, and the remaining liquid part will consist of

serum plus the blood-corpuscles. Blood which has been whipped in this way is known as "defibrinated blood." It resembles normal blood in appearance, but is different in its composition: it cannot clot again. The way in which the fibrin is normally deposited may be demonstrated most beautifully under the microscope by placing a good-sized drop of blood on a slide, covering it with a cover-slip, and allowing it to stand for several minutes until coagulation is completed. If the drop is now examined, it is possible by careful focussing to discover in the spaces between the masses of corpuscles many examples of the delicate fibrin network. The physiological value of clotting is that it stops hemorrhages by closing the openings of the wounded blood-vessels.

Time of Clotting.—The time necessary for the clot to form varies slightly in different individuals, or in the blood of the same individual varies with the conditions. It may be said in general that under normal conditions the blood passes into the jelly stage in from three to ten minutes. The separation of clot and serum takes place gradually, but is usually completed in from ten to forty-eight hours. The time of clotting shows marked variations in different animals; the process is especially slow in the horse and the terrapin, so that coagulation of shed blood is more easily prevented in these animals. In the human being also the time of clotting may be much prolonged under certain conditions—in fevers, for example. This fact was noticed in the days when bloodletting was a common practice. The slow clotting of the blood permitted the red corpuscles to sink somewhat, so that the upper part of the clot in such cases was of a lighter color, forming what was called the "buffy coat." The time of clotting may be shortened or be prolonged, or the clotting may be prevented altogether, in various ways, and much use has been made of this fact in studying the composition and the coagulation of blood as well as in controlling hemorrhages. It will be advantageous to postpone an account of these methods for hastening or retarding coagulation until the theories of coagulation have been considered.

Theories of Coagulation.—The clotting of blood is such a prominent phenomenon that it has attracted attention at all times, and as a result numerous theories to account for it have been advanced. Most of these theories possess simply an historical interest, and need not be discussed in a work of this character, but some reference to older views is unavoidable for a proper presentation of the subject. To prevent misunderstanding it may be stated explicitly in the beginning that there is at present no perfectly satisfactory theory. Indeed, the subject is a difficult one, as it is intimately connected with the chemistry of the proteids of the blood, and it may be said that a complete understanding of clotting waits upon a better knowledge of the nature of these proteids. It happens that at the present time a great deal of attention is being paid to this subject by experimenters, and it is possible that at any moment new facts may be discovered which will alter present ideas of the nature of the process. In considering the different theories that have been proposed there are two general facts which should always be kept in mind: first, that the main phenomenon

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which a theory of coagulation has to explain is the formation of fibrin ; second, that all theories unite in the common belief that the fibrin is derived, in part at least, from the fibrinogen of the plasma.

Schmidt's Older Theory of Coagulation.—The first theory which gained general acceptance in recent times was that of Alexander Schmidt. It was proposed in 1861, and it has served as the basis for all subsequent theories. Schmidt held that the fibrin of the clot is formed by a reaction between para-globulin (he called it " fibrinoplastin ") and fibrinogen, and that this reaction is brought about by a third body, to which he gave the name of *fibrin ferment.* Fibrin ferment was believed to be absent from normal blood, but to be formed after the blood was shed. Further reference will presently be made to the nature of this substance. Schmidt was not able to determine its nature— whether it was a proteid or not—but he discovered a method of preparing it from blood-serum, and demonstrated that it cannot be obtained from blood immediately after it leaves the blood-vessels, and that consequently it does not exist in circulating blood, in any appreciable quantity at least. Finally, Schmidt believed that a certain quantity of soluble salts is necessary as a fourth " fibrin factor."

Hammarsten's Theory of Coagulation.—Hammarsten, who repeated Schmidt's experiments, demonstrated that paraglobulin is unnecessary for the formation of fibrin. He showed that if a solution of pure fibrinogen is prepared, and if there is added to it a solution of fibrin ferment entirely free from paraglobulin, a typical clot is formed. This experiment has since been confirmed by others, so that at present it is generally accepted that paraglob-ulin takes no direct part in the formation of fibrin. Hammarsten's theory is that there are two fibrin factors, fibrin ferment and fibrinogen, and that fibrin results from a reaction between these two bodies. The nature of this reaction could not be determined, but Hammarsten showed that the entire fibrinogen molecule is not changed to fibrin. A dissociation or splitting occurs, so that in place of the fibrinogen there is present after clotting, on the one hand, fibrin representing most of the weight of fibrinogen, and, on the other hand, a newly-formed globulin-like proteid retained in solution in the serum, to which proteid the name *fibrin-globulin* has been given. Ham-marsten supposed that although paraglobulin took no direct part in the process, it acted as a favoring condition, a greater quantity of fibrin being formed when it was present. Some recent experiments [1] show that this supposition is incorrect, and that paraglobulin may be eliminated entirely from the theory. The theory of Hammarsten, which is perhaps generally accepted at the present time, is incomplete, however, in that it leaves undetermined the nature of the ferment and of the reaction between it and the fibrinogen. The aim of the newer theories has been to supply this deficiency.

Schmidt's Recent Theory of Coagulation.—In a recent book [2] containing the results of a lifetime of work devoted to the study of blood-coagulation,

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[1] Frederikse: *Zeitschrift für physiologische Chemie,* vol. 19, 1894, p. 143.

[2] *Zur Blutlehre,* Leipzig, 1893.

Schmidt has modified his well-known theory. His present ideas of the direct and indirect connection of the proteids of the plasma with the formation of fibrin are too complex to be stated clearly in brief compass. He classifies the conditions necessary for coagulation as follows : (1) Certain soluble proteids—namely, the two globulins of the blood—as the material from which fibrin is made. Schmidt does not believe, however, that paraglobulin and fibrinogen react to make fibrin, but believes that fibrinogen is formed from paraglobulin, and that fibrinogen in turn is changed to fibrin. (2) A specific ferment, fibrin ferment, to effect the changes in the proteids just stated. He proposes for fibrin ferment the distinctive name of *thrombin*. (3) A certain quantity of neutral salts is necessary for the precipitation of the fibrin in an insoluble form.

The Relation of Calcium Salts to Coagulation.—It has been shown by a number of observers that calcium salts take an important part in the process of clotting. This fact was most clearly demonstrated by Arthus and Pages, who found that if oxalate of potash or soda is added to freshly-drawn blood in quantities sufficient to precipitate the calcium salts, clotting will be prevented. If, however, a soluble calcium salt is again added, clotting occurs promptly. This fact has been demonstrated not only for the blood, but also for pure solutions of fibrinogen, and we are justified in saying that without the presence of calcium salts fibrin cannot be formed from fibrinogen. This is one of the most significant facts recently brought out in connection with coagulation. We know that fibrinogen when acted upon by fibrin ferment produces fibrin, but we now know also that calcium salts must be present. What is the relation of these salts to the so-called " ferment "? This question has been differently answered in two recent theories of coagulation.

Pekelharing's Theory of Coagulation.—Pekelharing[1] succeeded in separating from blood-plasma a proteid body which has the properties of a nucleo-albumin. He finds that if this substance is brought into solution together with fibrinogen and calcium salts, a typical clot will form, while nucleo-albumin alone, or calcium salts alone, added to fibrinogen solutions, cause no clotting. His theory of coagulation is that what has been called " fibrin ferment " is a compound of nucleo-albumin and calcium, and that when this compound is brought into contact with fibrinogen a reaction occurs, the calcium passing over to the fibrinogen and forming an insoluble calcium compound, fibrin. According to this theory, fibrin is a calcium compound with fibrinogen or with a part of the fibrinogen molecule. This idea is strengthened by the unusually large percentage of calcium found in fibrin ash. The theory supposes also that the fibrin ferment is not present in blood-plasma—that is, in sufficient quantity to set up coagulation—but that it is formed after the blood is shed. The nucleo-albumin part is derived from the corpuscles of the blood (leucocytes, blood-plates), which break down and go into solution. This nucleo-albumin then unites with the calcium salts present in the blood to form fibrin ferment, an organic compound of calcium capable of reacting with fibrinogen. The theory is a simple one; it accounts for the

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[1] *Untersuchungen über das Fibrinferment*, Amsterdam, 1892.

importance of calcium salts in coagulation, and reduces the interchange between fibrinogen and fibrin ferment to the nature of an ordinary chemical reaction.

Lilienfeld's Theory of Coagulation.—Lilienfeld[1] has carried still further the chemical study of the changes occurring in coagulation. Like Pekelharing he finds that the three important substances to be considered in coagulation are fibrinogen, nuclein compounds, and calcium salts. He differs from Pekelharing, however, in his description of how these substances react with one another in producing fibrin. Lilienfeld and others have shown that a compound proteid to which the name "nucleohiston" is given may be extracted from the nuclei of leucocytes and other cells, and that this neucleohiston under some circumstances favors the coagulation of liquids containing fibrinogen, but under other circumstances prevents or retards coagulation. Nucleohiston is readily decomposed into its two constituents—histon, a proteid body, and a nucleo-proteid to which the specific name of "leuconuclein" is given. Histon when injected into the blood of a living animal has a remarkable influence in preventing coagulation: blood drawn shortly after the injection remains perfectly fluid, and its histological elements, red and white corpuscles and blood-plates, retain perfectly their normal shapes. Leuconuclein, on the contrary, although it is not able to produce fibrin from fibrinogen, does cause the fibrinogen molecule to split, with the formation of a substance, "thrombosin," which comes down as a precipitate. If this thrombosin is dissolved in dilute alkaline solution it clots readily when brought into contact with calcium salts. Thrombosin may also be formed from fibrinogen by the action of dilute acetic acid or nucleic acid (nuclein). Normal coagulation, according to Lilienfeld, takes place as follows: After blood is shed there occurs a disintegration of leucocytes (and blood-plates) resulting in the giving off of nuclein compounds to the plasma. These nuclein substances, being dissolved in the alkaline plasma, come in contact with the fibrinogen and decompose it, with the formation of thrombosin. This latter substance then unites with the calcium salts of the plasma to form fibrin, which, on this theory, might be defined as a calcium compound of thrombosin. Lilienfeld's theory does not give a satisfactory explanation of the nature of fibrin ferment, but is very valuable in demonstrating that the essential act of clotting—that is, of the formation of fibrin—is the union of calcium salts with a portion of the fibrinogen molecule, and that this portion of the fibrinogen molecule may first be split off by the action of acetic acid or the acid nuclein compounds. Until further investigations are made it is not possible to decide between the theories of Pekelharing and Lilienfeld. It is well, however, to emphasize the fact that there is much in common between the two theories. Each holds that the fibrin is a compound of calcium salts with a portion of the fibrinogen molecule, the latter undergoing splitting during the act of clotting. According to Lilienfeld, this splitting of the fibrinogen molecule is caused by nucleo-proteid, and the thrombosin thus formed then combines with the calcium. According to Pekel-

[1] *Du Bois-Reymond's Archiv für Physiologie*, 1893, p. 560.

haring, the nucleo-proteid first combines with the calcium, and then this cal-
cium compound reacts with the fibrinogen, transferring its calcium to a portion
of the molecule. We might say, therefore, that there are three fibrin factors
—fibrinogen, nucleo-proteid, and calcium salts; the first and last of these exist
in the circulating blood, but the nucleo-proteid is formed usually only after
the blood is shed, and is derived from the disintegration of the formed ele-
ments, the leucocytes and blood-plates. How these three factors interact to
form fibrin cannot be stated positively, but it seems to be satisfactorily deter-
mined that the fibrin is a compound of calcium with a product derived from
the splitting of the fibrinogen.

Nature and Origin of Fibrin Ferment (Thrombin).—Recent views as
to the nature of fibrin ferment have been referred to incidentally in the
description of the theories of coagulation just given. The relation of these
newer views to the older ideas can be presented most easily by giving a
brief description of the development of our knowledge concerning this body.
Schmidt prepared solutions of fibrin ferment originally by adding a large
excess of alcohol to blood-serum and allowing the proteids thus precipitated
to stand under strong alcohol for a long time until they were thoroughly coagu-
lated and rendered nearly insoluble in water. At the end of the proper period
the coagulated proteids were extracted with water, and there was obtained a
solution which contained only small quantities of proteid. It was found that
solutions prepared in this way had a marked effect in inducing coagulation
when added to liquids, such as hydrocele liquid, which contained fibrinogen,
but which did not clot spontaneously or else clotted very slowly. It was after-
ward shown that similar solutions of fibrin ferment are capable of setting up
coagulation very readily in so-called salted plasma—that is, in blood-plasma
prevented from clotting by the addition of a certain quantity of neutral salts.
It was not possible to say whether the coagulating power of these solutions
was due to the small traces of proteid contained in them, or whether the pro-
teid was merely an impurity. The general belief for a time, however, was
that the proteids present were not the active agent, and that there was in solu-
tion something of an unknown chemical nature which acted upon the fibrinogen
after the manner of unorganized ferments. This belief was founded mainly
upon three facts: first, that the substance seemed to be able to act powerfully
upon fibrinogen, although present in such minute quantities that it could not be
isolated satisfactorily; second, it was destroyed by heating its solutions for a few
minutes at 60° C.; and, third, it did not seem to be destroyed in the reaction
of coagulation which it set up, since it was always present in the serum squeezed
out of the clot. Schmidt proved that fibrin ferment could not be obtained
from blood by the method described above if the blood was made to flow im-
mediately from the cut artery into the alcohol. On the other hand, if the shed
blood was allowed to stand, the quantity of fibrin ferment increased up to
the time of coagulation, and was present in quantity in the serum. Schmidt
believed that the ferment was formed in shed blood from the disintegration
of the leucocytes, and this belief was corroborated by subsequent histological

work. It was shown in microscopic preparations of coagulated blood that the fibrin threads often radiated from broken-down leucocytes—an appearance which seemed to indicate that the leucocytes served as points of origin for the deposition of the fibrin. When the blood-plates were discovered a great deal of microscopic work was done tending to show that these bodies also are connected with coagulation in the same way as the leucocytes, and serve probably as sources of fibrin ferment. In microscopic preparations the fibrin threads were found to radiate from masses of partially disintegrated plates; and, moreover, it was discovered that conditions which retard or prevent coagulation of blood often serve to preserve the delicate plates from disintegration. At the present time it is generally believed that there is derived from the disintegration of the leucocytes and blood-plates something which is necessary to the coagulation of blood, but there is some difference of opinion as to the nature of this substance and whether it is identical with Schmidt's fibrin ferment. Pekelharing thinks that the substance set free from the corpuscles and plates is a nucleo-proteid, but that this nucleo-proteid is not capable of acting upon fibrinogen until it has combined with the calcium salts of the blood. According to his view, therefore, fibrin ferment, in Schmidt's sense, is a compound of calcium and nucleo-proteid. Lilienfeld has shown by chemical reactions that blood-plates and nuclei of leucocytes contain nucleo-proteid material which in all probability is liberated in the blood-plasma by the disintegration of these elements after the blood is shed. As he has shown also that this nucleo-proteid material with the aid of calcium salts acts upon the fibrinogen to produce fibrin, it would seem clear that the so-called fibrin ferment is really a nucleo-proteid compound. Lilienfeld contends, however, that solutions of fibrin ferment prepared by Schmidt's method do not contain any nucleo-proteid material, and that, although the liberation of the nucleo-proteid material is what starts normal coagulation of blood, nevertheless so-called fibrin ferment is something entirely different from nucleo-proteid. In this point, however, his results are contradicted by the experiments of Pekelharing and of Halliburton, who both find that solutions of fibrin ferment prepared by Schmidt's method give distinct evidence of containing nucleo-proteid material. We may conclude, therefore, that the essential element of Schmidt's fibrin ferment is a nucleo-proteid compound. Whether or not this nucleo-proteid can act upon fibrinogen directly, as Lilienfeld claims, or must first combine with calcium salts, as held by Pekelharing, is a matter which must be left to future investigation.

Intravascular Clotting.—Clotting may be induced within the blood-vessels by the introduction of foreign particles, either solid or gaseous—for example, air—or by injuring the inner coat of the blood-vessels, as in ligating. In the latter case the area injured by the ligature acts as a foreign surface and probably causes the disintegration of a number of corpuscles. The clot in this case is confined at first to the injured area, and is known as a "thrombus." Intravascular clotting more or less general in occurrence may be produced by injecting into the circulation such substances as leucocytes obtained by macerating lymph-glands, extracts of fibrin ferment, solutions of

nucleo-albumins of different kinds, etc. According to the theory of coagulation adopted above, injections of these latter substances ought to cause coagulation very readily, since the blood already contains fibrinogen, and needs only the presence of ferment to set up coagulation. As a matter of fact, however, intravascular clotting is produced with some difficulty by these methods, showing that the body can protect itself within certain limits from an excess of ferment in the circulating blood. Just how this is done is not known, but possibly it is due to some defensive activity of the living endothelial cells lining the interior of the blood-vessels. Moreover, injection of leucocytes, nucleo-albumins, etc. sometimes diminishes instead of increasing the coagulability of blood, making the so-called "negative phase" of the injection. In the case of leucocytes it is probable that this result is accounted for by the fact that the nucleohiston liberated by their disintegration may undergo decomposition in the blood with the formation of histon, which is known to prevent coagulation (see p. 356).

Why Blood does not Clot within the Blood-vessels.—The reasons why blood remains fluid while in the living blood-vessels, but clots quickly after being shed or after being brought into contact with a foreign substance in any way, have already been stated in describing the theories of coagulation, but they will be restated here in more categorical form. Briefly, then, blood does not clot within the blood-vessels because nucleo-proteids are not present in sufficient quantities at any one time. Leucocytes and blood-plates probably disintegrate here and there within the circulation, but the small amount of ferment thus formed is insufficient to act upon the blood, and probably the ferment is quickly destroyed or changed. When blood is shed, however, the formed elements break down in mass, as it were, liberating a relatively large amount of nucleo-proteids, which, in combination with the calcium salts, produce fibrin from the fibrinogen. In shed blood the restraining action of the endothelial cells of the blood-vessels, a more or less unknown factor, is also eliminated.

Means of Hastening or of Retarding Coagulation.—Blood coagulates normally within a few minutes, but the process may be hastened by increasing the extent of foreign surface with which it comes in contact. Thus, moving the liquid when in quantity, or the application of a sponge or a handkerchief to a wound, will hasten the onset of clotting. This is easily understood when it is remembered that nucleo-proteids arise from the breaking down of leucocytes and blood-plates, and that these corpuscles go to pieces more rapidly when in contact with a dead surface. It has been proposed also to hasten clotting in case of hemorrhage by the use of ferment solutions. Hot sponges or cloths applied to a wound will hasten clotting, probably by accelerating the formation of ferment and the chemical changes of clotting. Coagulation may be retarded or be prevented altogether by a variety of means, of which the following are the most important:

1. *By Cooling.*—This method succeeds well only in blood which clots slowly—for example, the blood of the horse or the terrapin. Blood from these animals received into narrow vessels surrounded by crushed ice may be

kept fluid for an indefinite time. The blood-corpuscles soon sink, so that this method is an excellent one for obtaining pure blood-plasma. The cooling probably prevents clotting by keeping the corpuscles intact.

2. *By the Action of Neutral Salts.*—Blood received at once from the blood-vessels into a solution of such neutral salts as sodium sulphate or magnesium sulphate, and well mixed, will not clot. In this case also the corpuscles settle slowly, or they may be centrifugalized, and specimens of plasma can be obtained. For this purpose horse's or cat's blood is to be preferred. Such plasma is known as "salted plasma;" it is frequently used in experiments in coagulation—for example, in testing the efficacy of a given ferment solution. The best salt to use is $MgSO_4$ in solutions of 27 per cent.: 1 part by volume of this solution is usually mixed with 4 parts of blood; if cat's blood is used a smaller amount may be taken—1 part of the solution to 9 of blood. Salted plasma or salted blood again clots when diluted sufficiently with water or when ferment solutions are added to it. How the salts prevent coagulation is not definitely known—possibly by preventing the disintegration of corpuscles and the formation of ferment, possibly by altering the chemical properties of the proteids.

3. *By the Action of Albumose Solutions.*—Certain of the products of proteid digestion, peptones and albumoses, when injected into the circulation retard clotting for a long time. For injection into dogs one uses 0.3 gram to each kilogram of animal. If the blood is withdrawn shortly after the injection, it will remain fluid for a long time. According to Pekelharing, the albumoses act by combining with the calcium salts, or at least by preventing them from reacting normally.

4. *By the Use of Leech Extracts.*—Extract of the heads of leeches, when mixed with blood, will prevent coagulation. The extract contains some substance formed in the salivary glands of the leech. It is probable that this substance acts normally to prevent the clotting of blood when sucked in by the animal.

5. *By the Action of Oxalate Solutions.*—If blood as it flows from the vessels is mixed with solutions of potassium or sodium oxalate in proportion sufficient to make a total strength of 0.1 per cent. or more of these salts, coagulation will be prevented entirely. Addition of an excess of water will not produce clotting in this case, but solutions of some soluble calcium salt will quickly start the process. The explanation of the action of the oxalate solutions is simple: they are supposed to precipitate the calcium as insoluble calcium oxalate.

Total Quantity of Blood in the Body.—The total quantity of blood in the body has been determined approximately for man and a number of the lower animals. The method used in such determinations consists essentially in first bleeding the animal as thoroughly as possible and weighing the quantity of blood thus obtained, and afterward washing out the blood-vessels with water and estimating the amount of hæmoglobin in the washings. The results are as follows: Man, 7.7 per cent. ($\frac{1}{13}$) of the body-weight; that is, a man

weighing 68 kilos. has about 5236 grams, or 4965 c.c., of blood in his body; dog, 7.7 per cent.; rabbit and cat, 5 per cent.; new-born human being, 5.26 per cent.; and birds, 10 per cent. Moreover, the distribution of this blood in the tissues of the body at any one time has been estimated by Ranke,[1] from experiments on freshly-killed rabbits, as follows:

Spleen	0.23	per cent.
Brain and cord	1.24	" "
Kidneys	1.63	" "
Skin	2.10	" "
Intestines	6.30	" "
Bones	8.24	" "
Heart, lungs, and great blood-vessels	22.76	" "
Resting muscles	29.20	" "
Liver	29.30	" "

It will be seen from inspection of this table that in the rabbit the blood of the body is distributed at any one time about as follows: one-fourth to the heart, lungs, and great blood-vessels; one-fourth to the liver; one-fourth to the resting muscles; and one-fourth to the remaining organs.

Regeneration of the Blood after Hemorrhage.—A large portion of the entire quantity of blood in the body may be lost suddenly by hemorrhage without producing a fatal result. The extent of hemorrhage which can be recovered from safely has been investigated upon a number of animals. Although the results show more or less individual variation, it can be said that in dogs a hemorrhage of from 2 to 3 per cent. of the body-weight[2] is recovered from easily, while a loss of 4.5 per cent., more than half the entire blood, will probably prove fatal. In cats a hemorrhage of from 2 to 3 per cent. of the body-weight is not usually followed by a fatal result. Just what percentage of loss can be borne by the human being has not been determined, but it is probable that a healthy individual may recover without serious difficulty from the loss of a quantity of blood amounting to as much as 3 per cent. of the body-weight. It is known that if liquids which are isotonic to the blood, such as a 0.9 per cent. solution of NaCl, are injected into the veins immediately after a severe hemorrhage, recovery will be more certain; in fact, it is possible by this means to restore persons after a hemorrhage which would otherwise have been fatal. The physiological reason for this fact seems to be that the large access of neutral liquid puts into circulation all the red corpuscles. Ordinarily the number of red corpuscles is greater than that necessary for a barely sufficient supply of oxygen, and increasing the bulk of liquid in the vessels after a severe hemorrhage makes more effective as oxygen-carriers the remaining red corpuscles, inasmuch as it ensures a more rapid circulation. If a hemorrhage has not been fatal, experiments on lower animals show that the plasma of the blood is regenerated with astonishing rapidity, the blood regaining its normal volume within a few hours in slight hemorrhages, and

[1] Taken from Vierordt's *Anatomische, physiologische und physikalische Daten und Tabellen,* Jena, 1893.

[2] Fredericq: *Travaux du Laboratoire (Université de Liége),* vol. i., 1885, p. 189.

in from twenty-four to forty-eight hours if the loss of blood has been severe; but the number of red corpuscles and the hæmoglobin are regenerated more slowly, getting back to normal only after a number of days or after several weeks.

Blood-transfusion.—Shortly after the discovery of the circulation of the blood (Harvey, 1628), the operation was introduced of transfusing blood from one individual to another or from some of the lower animals to man. Extravagant hopes were held as to the value of such transfusion not only as a means of replacing the blood lost by hemorrhage, but also as a cure for various infirmities and diseases. Then and subsequently, fatal as well as successful results followed the operation. It is now known to be a dangerous undertaking, mainly for two reasons: first, the strange blood, whether transfused directly or after defibrination, is liable to contain a quantity of fibrin ferment sufficient to cause intravascular clotting; secondly, the serum of one animal is known to cause often a destruction of the blood-corpuscles of another. Owing to this globulicidal action, which has previously been referred to (p. 334), the injection of foreign blood is likely to be directly injurious instead of beneficial. In cases of loss of blood from severe hemorrhage, therefore, it is far safer to inject a neutral liquid, such as the so-called "physiological salt-solution"—a solution of NaCl of such a strength (0.9 per cent.) as to be isotonic to the corpuscles. The bulk of the circulating liquid is thereby augmented, and all the red corpuscles are made more efficient as oxygen-carriers, partly owing to the fact that the velocity of the circulation is increased, and partly because the corpuscles are kept from stagnation in the capillary areas.

LYMPH.

Lymph is a colorless liquid found in the lymph-vessels as well as in the extravascular spaces of the body. All the tissue-elements, in fact, may be regarded as being bathed in lymph. To understand its occurrence in the body one has only to bear in mind its method of origin from the blood. Throughout the entire body there is a rich supply of blood-vessels penetrating every tissue with the exception of the epidermis and some epidermal structures, as the nails and the hair. The plasma of the blood filters through, or is secreted through, the thin walls of the capillaries, and is thus brought into immediate contact with the tissues, to which it brings the nourishment and oxygen of the blood and from which it removes the waste products of metabolism. This extravascular lymph is collected into small capillary spaces which in turn open into definite lymphatic vessels. These vessels unite to larger and larger trunks, forming eventually one main trunk, the thoracic or left lymphatic duct, and a second smaller right lymphatic duct, which open into the blood-vessels, each on its own side, at the junction of the subclavian and internal jugular veins. The lymph movement is from the tissues to the veins, and the flow is maintained chiefly by the difference in pressure between the lymph at its origin in

the tissues and in the large lymphatic vessels. The continual formation of lymph in the tissues leads to the development of a relatively high pressure in the lymph capillaries, and as a result of this the lymph is forced toward the point of lowest pressure—namely, the points of junction of the large lymph-ducts with the venous system. A fuller discussion of the factors concerned in the movement of lymph will be found in the section on Circulation. As would be inferred from its origin, the composition of lymph is essentially the same as that of blood-plasma. Lymph contains the three blood-proteids, the extractives (urea, fat, lecithin, cholesterin, sugar), and inorganic salts. The salts are found in the same proportions as in the plasma; the proteids are less in amount, especially the fibrinogen. Lymph coagulates, but does so more slowly and less firmly than the blood. Histologically, lymph consists of a colorless liquid containing a number of leucocytes, and after meals a number of minute fat-droplets; red blood-corpuscles occur only accidentally, and blood-plates, according to most accounts, are likewise normally absent.

Formation of Lymph.—The careful researches of Ludwig and his pupils were formerly believed to prove that the lymph is derived directly from the plasma of the blood by filtration through the capillary walls. Various conditions which alter the pressure of the blood were shown to influence the amount of lymph formed in accordance with the demands of a theory of filtration. Moreover, the composition of lymph as usually given seems to support such a theory, inasmuch as the inorganic salts contained in it are in the same concentration, approximately, as in blood-plasma, while the proteids are in less concentration, following the well-known law that in the filtration of colloids through animal membranes the filtrate is more dilute than the original solution. This simple and apparently satisfactory theory has been subjected to critical examination within recent years, and it has been shown that filtration alone does not suffice to explain the composition of the lymph under all circumstances. At present two divergent views are held upon the subject. According to some physiologists, all the facts known with regard to the composition of lymph may be satisfactorily explained if we suppose that this liquid is formed from blood-plasma by the combined action of the two physical processes of filtration and diffusion. According to others, it is believed that, in addition to filtration and diffusion, it is necessary to assume an active secretory process on the part of the endothelial cells composing the capillary walls. A discussion upon these points is in progress at present in current physiological literature, and it is impossible to foresee definitely what the outcome will be, since a final conclusion can be reached only by repeated experimental investigations. The actual condition of our knowledge of the subject can be presented most easily by briefly stating the objections which have been raised by Heidenhain[1] to a pure filtration-and-diffusion theory, and indicating how these objections have been met.

1. Heidenhain shows by simple calculations that an impossible formation of lymph would be required, upon the filtration theory, to supply the chemical

[1] *Archiv für die gesammte Physiologie*, 1891, Bd. xlix. S. 209.

needs of the organs in various organic and inorganic constituents. Thus, to take an illustration which has been much discussed, one kilogram of cow's milk contains 1.7 grams CaO, and the entire milk of twenty-four hours would contain in round numbers 42.5 grams CaO. Since the lymph contains normally about 0.18 parts of CaO per thousand, it would require 236 liters of lymph per day to supply the necessary CaO to the mammary glands. Heidenhain himself suggests that the difficulty in this case may be met by assuming active diffusion processes in connection with filtration. If, for instance, in the case cited, we suppose that the CaO of the lymph is quickly combined by the tissues of the mammary gland, then the tension of calcium salts in the lymph will be kept at zero, and an active diffusion of calcium into the lymph will occur so long as the gland is secreting. In other words, the gland will receive its calcium by much the same process as it receives its oxygen, and will get its daily supply from a comparatively small bulk of lymph. Cohnstein [1] has answered the problem in another way. He calls attention to the fact that in the body the capillaries contain blood under a comparatively high pressure, while on their exterior they are bathed with lymph, also under pressure, although less than that of the blood. The pressure causing filtration in this case is the difference in pressure between the inside and the outside liquid. Moreover these liquids differ in composition, so that diffusion must also take place in such a manner that crystalloids will diffuse out into the lymph, and an amount of water corresponding to the osmotic equivalent will pass into the blood. The lymph that is actually formed will therefore be the balance between these two processes, and a liquid produced in this way he designates specifically as a transudation. From laboratory experiments made with ureters and veins he shows that the percentage composition of the transudation in crystalloid substances will increase with the pressure of the outside liquid. As this pressure is raised the filtration-stream is diminished, but the diffusion is unaffected, hence the transudation will be more concentrated. It is possible in this way, as he shows by experiment, to get a transudation much more concentrated than the original liquid, and he assumes that in the body the lymph formed in the tissues may be more concentrated than the blood, and thus a small quantity of lymph may transport a large amount of crystalloid substance. What seems to be a fatal objection to this reasoning, so far as it applies to the difficulty first suggested with regard to the chemical needs of the organs, is the time element. As Heidenhain points out, the more concentrated the transudation the less its bulk, so that to get the required amount of CaO, for example, would upon this hypothesis require much more than twenty-four hours. Strictly speaking, however, the difficulty we are dealing with here shows only the insufficiency of a pure filtration theory. It seems possible that filtration and diffusion together would suffice to supply the organs, so far at least as the diffusible substances are concerned.

2. Heidenhain found that occlusion of the inferior vena cava causes not only an increase in the flow of lymph—as might be expected, on the filtration

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[1] *Archiv für die gesammte Physiologie,* 1894, Bd. lix. S. 350.

theory, from the consequent rise of pressure in the capillary regions—but also an increased concentration in the percentage of proteid in the lymph. This latter fact has been satisfactorily explained by the experiments of Starling.[1] According to this observer, the lymph formed in the liver is normally more concentrated than that of the rest of the body. The occlusion of the vena cava causes a marked rise in the capillary pressure in the liver, and most of the increased lymph-flow under these circumstances comes from the liver, hence the greater concentration. The results of this experiment, therefore, do not antagonize the filtration-and-diffusion theory.

3. Heidenhein discovered that extracts of various substances which he designated as " lymphagogues of the first class " cause a marked increase in the flow of lymph from the thoracic duct, the lymph being more concentrated than normal, and the increased flow continuing for a long period. Nevertheless, these substances cause little, if any, increase in general arterial pressure; in fact, if injected in sufficient quantity they produce usually a fall of arterial pressure. The substances belonging to this class comprise such things as peptone, egg-albumin, extracts of liver and intestine, and especially extracts of the muscles of crabs, crayfish, mussels, and leeches. Heidenhain supposes that these extracts contain an organic substance which acts as a specific stimulus to the endothelial cells of the capillaries and increases their secretory action. The results of the action of these substances has been differently explained by those who are unwilling to believe in the secretion theory. Starling[2] finds experimentally that the increased flow of lymph in this case, as after obstruction of the vena cava, comes mainly from the liver. There is at the same time in the portal area an increased pressure which may account in part for the greater flow of lymph; but, since this effect upon the portal pressure lasts but a short time, while the greater flow of lymph may continue for one or two hours, it is obvious that this factor alone does not suffice to explain the result of the injections. Starling suggests, therefore, that these extracts act pathologically upon the blood-capillaries, particularly those of the liver, and render them more permeable, so that a greater quantity of concentrated lymph filters through them. No experimental proof is given to show that these extracts do so affect the capillary walls. Starling's explanation is supported by the experiments of Popoff.[3] According to this observer, if the lymph is collected simultaneously from the lower portions of the thoracic duct, which conveys the lymph from the abdominal organs, and from the upper part, which contains the lymph from the head, neck, etc., it will be found that injection of peptone increases the flow only from the abdominal organs. Popoff finds also that the peptone causes a dilatation in the intestinal circulation and a marked rise in the portal pressure. At the same time there is some evidence of injury to the walls of the blood-vessels from the occurrence of extravasation in the intestine. Cohnstein,[4] from experiments made with peptone solu-

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[1] *Journal of Physiology*, 1894, vol. xvi. p. 234. [2] *Ibid.*, 1894, vol. xvii. p. 30.

[3] *Centralblatt für Physiologie*, 1895, Bd. ix., No. 2.

[4] *Archiv für die gesammte Physiologie*, 1894, Bd. lix. S. 366.

tions, suggests a different explanation of the action of these lymphagogues. He believes that these substances diminish in some way the osmotic tension of the blood. In consequence of this diminution the diffusion-stream of water from lymph into the blood is lessened, and therefore the filtration-stream in the opposite direction, if it remains unchanged, must cause an increased volume of lymph. This, theory, although supported to some extent by experimental evidence, does not seem to explain the greater concentration of lymph obtained in these cases. So far, however, as the action of the lymphagogues of the first class is concerned, it may be said that the advocates of the filtration-and-diffusion theory have suggested a plausible explanation in accord with their theory. The facts emphasized by Heidenhain with regard to this class of substances do not compel us to assume a secretory function for the endothelial cells.

4. Injection of certain crystalline substances, such as sugar, NaCl, and other neutral salts, causes a marked increase in the flow of lymph from the thoracic duct. The lymph in these cases is more dilute than normal, and the blood-plasma also becomes more watery, thus indicating that the increase in water comes from the tissues themselves. Heidenhain designated these bodies as "lymphagogues of the second class." His explanation of their action is that the crystalloid materials introduced into the blood are eliminated by the secretory activity of the endothelial cells, and that they then attract water from the tissue-elements, thus augmenting the flow of lymph. These substances cause but little change in arterial blood-pressure, hence Heidenhain thought that the greater flow of lymph could not be explained by an increased filtration. Starling[1] has shown, however, that, although these bodies may not seriously alter general arterial pressure, they may greatly augment intracapillary pressure, particularly in the abdominal organs. His explanation of the greater flow of lymph in these cases is as follows: "On their injection into the blood the osmotic pressure of the circulating fluid is largely increased. In consequence of this increase water is attracted from lymph and tissues into the blood by a process of osmosis, until the osmotic pressure of the circulating fluid is restored to normal. A condition of hydræmic plethora is thereby produced, attended with a rise of pressure in the capillaries generally, especially in those of the abdominal viscera. This rise of pressure will be proportional to the increase in the volume of the blood, and therefore to the osmotic pressure of the solutions injected. The rise of capillary pressure causes great increase in the transudation of fluid from the capillaries, and therefore in the lymph-flow from the thoracic duct." This explanation is well supported by experiments, and seems to obviate the necessity of assuming a secretory action on the part of the capillary walls.

5. One of the most interesting facts developed by the experiments of Heidenhain and his pupils is that after the injection of sugar or neutral salts in the blood the percentage of these substances in the lymph of the thoracic duct may be greater than in the blood itself. It is obviously difficult to explain how this can occur by filtration or diffusion, since it seems to involve the pas-

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[1] *Op. cit.*

sage of crystalloid bodies from a less concentrated to a more concentrated solution. Cohnstein [1] has endeavored to show a fallacy in these results. He contends that since it requires some time (several minutes) for the lymph to form and pass into the thoracic duct, it is not justifiable to compare the quantitative composition of specimens of blood and lymph taken at the same time. If one compares, in any given experiment, the maximal percentage in the blood of the substance injected with its maximal percentage in the lymph, the latter will be found to be lower. This, however, does not seem to be the case in all the experiments reported. The work of Mendel [2] with sodium iodide seems to establish the fact that when this salt is injected slowly its maximal percentage in the lymph may exceed that in the blood; and in the experiments made by Cohnstein, as well as those by Mendel, it is shown that the percentage of the substance in the lymph remains above that in the blood throughout most of the experiment. In this point, therefore, there seems to be a real difficulty in the direct application of the laws of filtration and diffusion to the explanation of the composition of lymph. It is possible, however, that a better understanding of the conditions prevailing in the capillaries with regard to osmosis and filtration may clear up this difficulty. [3] Meanwhile it seems evident that in spite of the very valuable work of Heidenhain, which has added so much to our knowledge of the conditions influencing the formation of lymph, the existence of a definite secretory activity of the endothelial cells of the capillaries has not been proved.

[1] *Archiv für die gesammte Physiologie*, 1894–95, Bde. lix., lx. und lxii.
[2] *Journal of Physiology*, 1896, vol. xix. p. 227.
[3] See Hamberger: *Du Bois-Reymond's Archiv für Physiologie*, 1896, S. 36.

VII. CIRCULATION.

PART I.—THE MECHANICS OF THE CIRCULATION OF THE BLOOD AND OF THE MOVEMENT OF THE LYMPH.

A. GENERAL CONSIDERATIONS.

THE metaphorical phrase "circulation of the blood" means that every particle of blood, so long as it remains within the vessels, moves along a path which, no matter how tortuous, finally returns into itself; that, therefore, the particles which pass a given point of that path may be the same which have passed it many times already; and that the blood moves in its path always in a definite direction, and never in the reverse.

The discoverer of these weighty facts was "William Harvey, physician, of London," as he styled himself. In the lecture notes of the year 1616, mostly in Latin, which contain the earliest record of his discovery, he declares that a "perpetual movement of the blood in a circle is caused by the beat of the heart" ("perpetuum sanguinis motum in circulo fieri pulsu cordis").[1] For a long time afterward the name of the discoverer was coupled with the expression which he himself had introduced, and the true movement of the blood was known as the "Harveian circulation."[2]

Course of the Blood.—The metaphorical circle of the blood-path may be shown by such a diagram as Figure 93.

If, in the body of a warm-blooded animal, we trace the course of a given particle, beginning at the point where it leaves the right ventricle of the heart, we find that course to be as follows: From the trunk of the pulmonary artery (PA) through a succession of arterial branches derived therefrom into a capillary of the lungs (PC); out of that, through a succession of pulmonary veins, to one of the main pulmonary veins (PV) and the left auricle of the heart (LA); thence to the left ventricle (LV); to the trunk of the aorta (A); through a succession of arterial branches derived therefrom into any capillary (C) not supplied by the pulmonary artery; out of that, through a succession of veins (V) to one of the venæ cavæ or to a vein of the heart itself; thence to the right auricle (RA), to the right ventricle (RV), and to the trunk of the pulmonary artery, where the tracing of the circuit began.

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[1] William Harvey: *Prelectiones Anatomiæ Universalis*, edited, with an autotype reproduction of the original, by a committee of the Royal College of Physicians of London, 1886, p. 80.

[2] Harvey's discovery of the circulation was first published in the modern sense in his work *Exercitatio anatomica de motu cordis et sanguinis in animalibus*, Francofurti, 1628. This great classic can be read in English in the following: *On the Motion of the Heart and Blood in Animals*. By William Harvey, M. D.; Willis's translation, revised and edited by Alex. Bowie, 1889.

It must be noted here that a particle of blood which traverses a capillary of the spleen, of the pancreas, of the stomach, or of the intestines, and enters the portal vein, must next traverse a series of venous branches of diminishing size, and a capillary of the liver, before entering the succession of veins which will conduct the particle to the ascending vena cava (compare Figs. 93 and 94). Most of the blood, therefore, which leaves the liver has traversed two sets of capillaries, connected with one another by the portal vein, since quitting the arterial system. This ar-
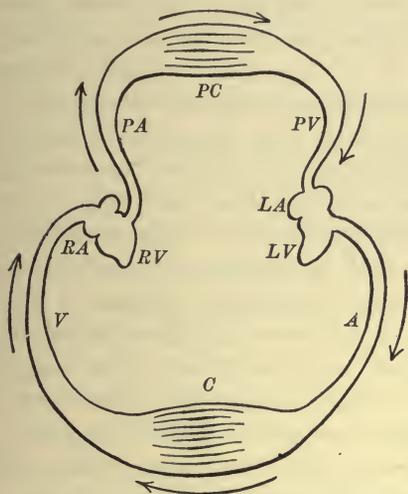
Fig. 93.—General diagram of the circulation: the arrows indicate the course of the blood: *P A*, pulmonary artery; *P C*, pulmonary capillaries; *P V*, pulmonary veins; *L A*, left auricle; *L V*, left ventricle; *A*, systemic arteries; *C*, systemic capillaries; *V*, systemic veins; *R A*, right auricle; *R V*, right ventricle.
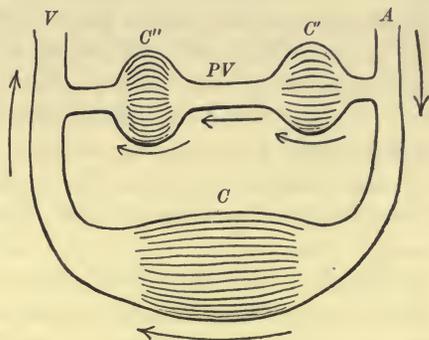
Fig. 94.—Diagram of the portal system: the arrows indicate the course of the blood: *A*, arterial system; *V*, venous system; *C'*, capillaries of the spleen, pancreas, and alimentary canal; *P V*, portal vein; *C''*, capillaries of the liver; *C*, the rest of the systemic capillaries. The hepatic artery is not represented.

rangement is of extreme importance for the physiology of nutrition. An arrangement of the same order, though less conspicuous, exists in the kidney.

Causes of the Blood-flow.—The force by which the blood is driven from the right to the left side of the heart through the capillaries which are related to the respiratory surface of the lungs, is nearly all derived from the contraction of the muscular wall of the right ventricle, which narrows the cavity thereof and ejects the blood contained in it; the force by which the blood is driven from the left to the right side of the heart through all the other capillaries of the body, often called the " systemic " capillaries, is derived nearly all from the contraction of the muscular wall of the left ventricle, which narrows its cavity and ejects its contents. The contractions of the two ventricles are simultaneous. The force derived from each contraction is generated by the conversion of potential energy, present in the chemical constituents of the muscular tissue, into energy of visible motion; a part also of the potential energy at the same time becoming manifest as heat. In the maintenance of the circulation the force generated by the heart is to a very subordinate degree supplemented by the forces which produce the aspiration of the chest and by

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the force generated by the contractions of the skeletal muscles throughout the body (see p. 387).

Mode of Working of the Pumping Mechanism.—During each contraction or "systole" of the ventricles the blood is ejected into the arteries only, because at that time the auriculo-ventricular openings are each closed by a valve. During the immediately succeeding "diastole" of the ventricles, which consists in the relaxation of their muscular walls and the dilatation of their cavities, blood enters the ventricles by way of the auricles only, because at that time the arterial openings are closed each by a valve which was open during the ventricular systole; and because the auriculo-ventricular valves which were closed during the systole of the ventricles are open during their diastole. During the first and longer part of the diastole of the ventricles the auricles, too, are in diastole; the whole heart is in repose; and blood is not only entering the auricles, but passing directly through them into the ventricles. Near the end of the ventricular diastole a brief simultaneous systole of both auricles takes place, during which they, too, narrow their cavities by the muscular contraction of their walls, and eject into the ventricles blood which had entered the auricles from the "systemic" and pulmonary veins respectively. The systole of the auricles ends immediately before that of the ventricles begins. The brief systole of the auricles is succeeded by their long diastole, which corresponds in time with the whole of the ventricular systole and with the greater part of the succeeding ventricular diastole. During the diastole of the auricles blood is entering them out of the veins. Thus it is seen that the direction in which the blood is forced is essentially determined by the mechanism of the valves at the apertures of the ventricles; and that it is due to these valves that the blood moves only in the definite direction before alluded to. In the words, again, of Harvey's note-book, at this point written in English, the blood is perpetually transferred through the lungs into the aorta " as by two clacks of a water bellows to rayse water."[1]

Pulmonary Blood-path.—In the birds and mammals the entire breadth of the blood-path, at one part of the physiological circle, consists in the capillaries spread out beneath the respiratory surface of the lungs. The right side of the heart exists only to force the blood into and past this portion of its circuit, where, as in the systemic capillaries, the friction due to the fineness of the tubes causes much resistance to the flow. This great comparative development of the pulmonary portion of the blood-path in the warm-blooded vertebrates is related to the activity, in them, of the respiration of the tissues, which calls for a corresponding activity of function at the respiratory surface of the lungs, and for a rapid renewal in every systemic capillary of the internal respiratory medium, the blood. This rapid renewal implies a rapid circulation; and that the speed is great with which the circuit of the heart and vessels is completed has been proven by experiment, the method being too complicated for description here.[2]

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[1] *Prelectiones*, etc., p. 80.

[2] Karl Vierordt: *Die Erscheinungen und Gesetze der Stromgeschwindigkeiten des Blutes.* 2te Ausgabe, 1882.

Rapidity of the Circulation.—By experiment the shortest time has been measured which is taken by a particle of blood in passing from a point in the external jugular vein of a dog to and through the right cavities of the heart, the pulmonary vessels, the left cavities of the heart, the commencement of the aorta, and the arteries, capillaries, and veins of the head, to the starting-point, or to the same point of the vein of the other side. This time has been found to be from fifteen to eighteen seconds. Naturally, the time would be different in different kinds of animals and in the different circuits in the same individual.

Order of Study of the Mechanics of the Circulation.—The significance and the fundamental facts of the circulation have now been indicated. Its phenomena must next be studied in detail.[1] As the blood moves in a circle, we may, in order to study the movement, strike into the circle at any point. It will, however be found both logical and instructive to study first the movement of the blood in the capillaries, whether systemic or pulmonary. It is only in passing through these and the minute arteries and veins adjoining that the blood fulfils its essential functions; elsewhere it is in transit merely. Moreover, it is only in the minute vessels that the blood and the nature of its movement are actually visible.

After the capillary flow shall have become familiar, it will be found that the other phenomena of the circulation will fall naturally into place as indicating how that flow is caused, is varied, and is regulated.

B. The Movement of the Blood in the Capillaries and in the Minute Arteries and Veins.

Characters of the Capillaries.—Each of the vessels which compose the immensely multiplied capillary network of the body is a tube, commonly of less than one millimeter in length, and of a few one-thousandths only of a millimeter in calibre, the wall of which is so thin as to elude accurate measure-

Fig. 95.—A capillary from the mesentery of the frog (Ranvier).

ment. The calibre of each capillary may vary from time to time. These facts indicate the minute subdivision of the blood-stream in the lungs, and among the tissues—that is, at the two points of its course where the essential functions of the blood are fulfilled. These facts also show the shortness of

[1] The following is a very valuable book of reference: Robert Tigerstedt: *Lehrbuch der Physiologie des Kreislaufes,* 1893.

the distance to be traversed by the blood while fulfilling these functions; and explain the importance of the comparatively slow rate at which it will be found to move through that short distance. The histological study of a typical capillary (see Fig. 95) shows that its thin wall is composed of a single layer only of living flat endothelial cells set edge to edge in close contact; and that the edges of the cells are united by a small quantity of the so-called cement-substance. If the capillary be traced in either anatomical direction, the wall of the vessel is seen to become less thin and more complex, till it merges into that of a typical arteriole or venule, the walls of which are still delicate, though less so than that of a capillary. That the capillary walls are so thin and soft, and are made of living cells, are very important facts as regards the relations between blood and tissue. It is of great importance for the variation of the blood-supply to a part that they are also distensible, elastic, and possibly contractile.

Direct Observation of the Flow in the Small Vessels.—The capillary flow is visible under the compound microscope, best by transmitted light, in the transparent parts of both warm-blooded and cold-blooded animals. It is important that the phenomena observed in the latter should be compared with observations upon the higher animals; but the fundamental facts can be most fruitfully studied in the frog, tadpole, or fish, inasmuch as no special arrangements are needed to maintain the temperature of the exposed parts of these animals. Moreover, their large oval and nucleated red blood-corpuscles are well fitted to indicate the forces to which they are subjected. The capillary movement, therefore, will be described as seen in the frog; it being understood that the phenomena are similar in the other vertebrates. In the frog the movement may be studied in the lung, the mesentery, the urinary bladder, the tongue, or the web between the toes. During such study the proper wall of the living capillary is hardly to be seen, but only the line on each side which marks the profile of its cavity. Even the proper walls of the transparent arterioles and venules are but vaguely indicated. The plasma of the blood, too, has so nearly the same index of refraction as the tissues, that it remains invisible. It is only the red corpuscles and leucocytes that are conspicuous; and when one speaks of seeing the blood in motion, he means, strictly speaking, that he sees the moving corpuscles, and can make out the calibre of the vessels in which they move. The observer uses as low a power of the microscope as will suffice, and takes first a general survey of the minute arteries, veins, and capillaries of the part he is studying, noting their form, size, and connections. In the arteries and veins he sees that the size of the vessels is ample in comparison with that of the corpuscles; that, in the veins, the movement of the blood is steady, but in the arteries accelerated and retarded, with a rhythm corresponding to that of the heart's beat. In the veins, moreover, the individual red corpuscles can be distinguished, while in the arteries they cannot, as at all times they shoot past the eye too swiftly. The fundamental observation now is verified that the blood is incessantly moving out of the arteries, through the capillaries, into the veins.

Behavior of the Red Corpuscles.—Capillaries will readily be found in which the red corpuscles move two or three abreast, or only in single file. They generally go with their long diameters parallel to, or moderately oblique to, the current. In no case will any blockade of corpuscles occur, so long as the parts are normal. The numerous red corpuscles are seen to be well fitted by their softness and elasticity, as well as by their form and size, for moving through the narrow channels. They bend easily upon themselves as they turn sharp corners, but instantly regain their form when free to do so (see Fig. 96). A very common occurrence is for a corpuscle to catch upon the edge which parts two capillaries at a bifurcation of the network. For some time the corpuscle may remain doubled over the projection like a sack thrown across a horse's back; but, after oscillating for a while, it will be disengaged, at once return to its own shape, and disappear in one of the two branches

FIG. 96.—To illustrate the behavior of red corpuscles in the capillaries: the arrows mark the course of the blood: *a*, a "saddle-bag" corpuscle; *b*, a corpuscle bending upon itself as it enters a side branch.
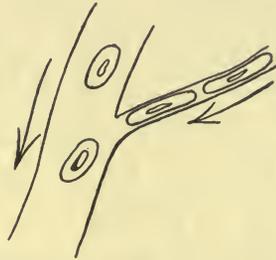
FIG. 97.—To illustrate the deformity produced in red corpuscles in passing through a capillary of a less diameter than themselves.

(see Fig. 96). It is instructive to watch red corpuscles passing in single file through a capillary the calibre of which, at the time, is actually less than the shorter diameter of the corpuscles. Through such a capillary each corpuscle is squeezed, with lengthening and narrowing of its soft mass, but on emerging into a larger vessel its elasticity at once corrects even this deformity; it regains its form, and passes on (Fig. 97).

Evidences of Friction.—In the minute vessels, capillary and other, certain appearances should carefully be observed which are the direct ocular evidence of that friction which we shall find to be one of the prime forces concerned in the blood-movement, to which it constitutes a strong resistance. If, in a channel which admits three red corpuscles beside one another, three be observed when just abreast, it will be found that very soon the middle one forges ahead, indicating that the stream is swiftest at its core. This is because the friction within the vessel is least in the middle, and progressively greater outward to the wall (Fig. 98). In the small veins the signs of friction are

strikingly seen, as the outer layers among the numerous corpuscles lag conspicuously. In the arterioles similar phenomena are seen if the normal swiftness of movement become sufficiently retarded for the individual corpuscles to be visible.
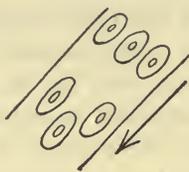
FIG. 98.—To illustrate the forging ahead of a corpuscle at the centre of the blood-stream. The arrow marks the direction of the blood.
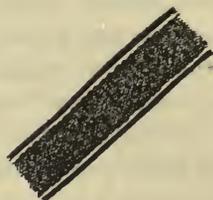
FIG. 99.—The inert layer of plasma in the small vessels.

An appearance which also tells of friction is that of the so-called "inert layer" of plasma.[1] In vessels, of whatever kind, which are wide enough for several corpuscles to pass abreast, it is seen that all the red corpuscles are always separated from the profile of their channel by a narrow clear and colorless interval—occupied, of course, by plasma. This is caused by the excess of the friction in the layers nearest to the vascular wall (see Fig. 99). The friction thus indicated, other things being equal, is less in a dilated than in a contracted tube; and less in a sluggish than in a rapid stream. It probably varies also with changes of an unknown kind in the condition of the cells of the vascular wall.

Behavior of the Leucocytes.—If the behavior of the leucocytes be watched, it will be seen to differ markedly from that of the red corpuscles, at least when the blood-stream is somewhat retarded, as it so commonly is under the microscope. Whereas the friction within the vessels causes the throng of red corpuscles to occupy the core of the stream, the scantier leucocytes may move mainly in contact with the wall, and thus be present freely in the inert layer of plasma. Naturally their progression is then much slower and more irregular than that of the red disks. Indeed, the leucocytes often adhere to the wall for a while, in spite of shocks from the red cells which pass them. Moreover, the spheroidal leucocyte rolls over and over as it moves along the wall in a way very different from the progression of the red disk, which only occasionally may revolve about one of its diameters. A leucocyte entangled among the red cells near the middle of the stream is seen generally not only to move onward but also to move outward toward the wall, and, before long, to join the other leucocytes which are bathed by the inert layer of plasma. It is due solely to the lighter specific gravity of the leucocytes that, under the forces at work within the smaller vessels, they go to the wall, while the denser disks go to the core of the current. This has been proved experimentally by driving through artificial capillaries a fluid having in suspension particles of two kinds. Those of the lighter kind go to the wall, of the heavier

[1] Poiseuille: "Recherches sur les causes du mouvement du sang dans les vaisseaux capillaires," *Académie des Sciences—Savans étrangers*, 1835.

kind to the core, even when the nature and form of the particles employed are varied.[1]

Emigration of Leucocytes.—It has been said that a leucocyte may often adhere for a time to the wall of the capillary, or of the arteriole or venule, in which it is. Sometimes the leucocyte not only adheres to the wall, but passes through it into the tissue without by a process which has received the name of "emigration."[2] A minute projection from the protoplasm of the leucocyte is thrust into the wall, usually where this consists of the soft cement-substance between the endothelial cells. The delicate pseudopod is seen presently to have pierced the wall, to have grown at the expense of the main body of the cell, and to have become knobbed at the free end which is in the tissue. Later, the flowing of the protoplasm will have caused the leucocyte to assume something of a dumb-bell form, with one end within the blood-vessel and the other without. Then, by converse changes, the flowing protoplasm comes to lie mainly within the lymph-space, with a small knob only within the vessel; and, lastly, this knob too flows out; what had been the neck of the dumb-bell shrinks and is withdrawn into the cell-body, and the leucocyte now lies wholly without the blood-vessel, while the minute breach in the soft wall has closed behind the retiring pseudopod. This phenomenon has been seen in capillaries, venules, and arterioles, but mainly in the two former. It seems to be due to the amœboid properties of the leucocytes as well as to purely physical causes. Emigration, although it may probably occur in normal vessels, is strikingly seen in inflammation, in which there seems to be an increased adhesiveness between the vascular wall and the various corpuscles of the blood.

Speed of the Blood in the Minute Vessels.—As a measure of the speed of the blood in a vessel, we may fairly take the speed of the red corpuscles. It must, however, be remembered that as the friction increases toward the wall, the speed of the red corpuscles is least in the outer layers of blood, and increases rapidly toward the long axis of the tube. At the core of the stream the speed may be twice as great as near the wall. As we have seen, the stream of red corpuscles in an arteriole is rapid and pulsating. In the corresponding venule, which is commonly a wider vessel, the stream is less swift, and its pulse has disappeared. In the capillary network between the two vessels the speed of the red corpuscles is evidently slower than in either arteriole or venule; and here, as in the veins, no pulse is to be seen; the pulse comes to an end with the artery which exhibits it. In one capillary of the network under observation the movement may be more active than in another; and even in a given capillary irregular variations of speed at different moments may be observed. Where two capillaries in which the pressure is nearly the same are connected by a cross-branch, the red corpuscles in this last may sometimes even be seen to

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[1] A. Schklarewsky: "Ueber das Blut und die Suspensionsflüssigkeiten," *Pflüger's Archiv für die gesammte Physiologie*, 1868, Bd. i. p. 603.

[2] For the literature of emigration see R. Thoma: *Text-book of General Pathology and Pathological Anatomy*, translated by A. Bruce, 1896, vol. i. p. 344.

oscillate, come to a standstill, and then reverse the direction of their move-
ment, and return to the capillary whence they had started. Naturally, no
such reversal will ever be seen in a capillary which springs directly from an
artery or which directly joins a vein. It will be remembered, however, that
any apparent speed of a corpuscle is much magnified by the microscope, and
that therefore the variations referred to are comparatively unimportant. We
may, in fact, without material error, treat the speed of the blood in the capil-
laries which intervene between the arteries and veins of a region as approxi-
mately uniform for an ordinary period of observation, as the minute varia-
tions will tend to compensate for one another. This speed is sluggish, as
already noted. In the capillaries of the web of the frog's foot it has been
found to be about 0.5 millimeter per second. The causes of this sluggishness
will be set forth later. That the very short distance between artery and vein
is traversed slowly, deserves to be insisted on, as thus time is afforded for the
uses of the blood to be fulfilled.

Capillary Blood-pressure.—The pressure of the blood against the capil-
lary wall is low, though higher than that of the lymph without. This pres-
sure is subject to changes, and is readily yielded to by the elastic and deli-
cate wall. From these changes of pressure changes of calibre result. The
microscope tells us less about the capillary blood-pressure than about the other
phenomena of the flow; but the microscope may sometimes show one striking
fact. In a capillary district under observation, a capillary not noted before
may suddenly start into view as if newly formed under the eye. This is
because its calibre has been too small for red corpuscles and leucocytes to enter,
until some slight increase of pressure has dilated the transparent tube, hitherto
filled with transparent plasma only. This dilatation has admitted corpuscles,
and has caused the vessel to appear.

That the capillary pressure is low is shown, moreover, by the fact that when
one's finger is pricked or slightly cut, the blood simply drips away; that it
does not spring in a jet, as when an artery of any size has been divided. That
the capillary pressure is low may also be shown, and more accurately, by the
careful scientific application of a familiar fact: If one press with a blunt
lead-pencil upon the skin between the base of a finger-nail and the neigh-
boring joint, the ruddy surface becomes pale, because the blood is expelled
from the capillaries and they are flattened. If delicate weights be used,
instead of the pencil, the force can be measured which just suffices to whiten
the surface somewhat, that is, to counterbalance the pressure of the distend-
ing blood, which pressure thus can be measured approximately. It has been
found to be very much lower than the pressure in the large arteries, con-
siderably higher than that in the large veins, and thus intermediate between
the two; whereas the blood-speed in the capillaries is less than the speed
in either the arteries or the veins. The pressure in the capillaries, meas-
ured by the method just described, has been found to be equal to that
required to sustain against gravity a column of mercury from 24 to 54 milli-

meters high ; or, in the parlance of the laboratory, has been found equal to from 24 to 54 millimeters of mercury.[1]

Summary of the Capillary Flow.—Whether in the lungs or in the rest of the body, the general characters of the capillary flow, as learned from direct inspection and from experiment, may be summed up as follows : The blood moves through the capillaries toward the veins with much friction, continuously, slowly, without pulse, and under low pressure. To account for these facts is to deal systematically with the mechanics of the circulation ; and to that task we must now address ourselves.

C. The Pressure of the Blood in the Arteries, Capillaries, and Veins.

Why does the blood move continuously out of the arteries through the capillaries into the veins? Because there is continuously a high pressure of blood in the arteries and a low pressure in the veins, and from the seat of high to that of low pressure the blood must continuously flow through the capillaries, where pressure is intermediate, as already stated.

Method of Studying Arterial and Venous Pressure, and General Results.—Before stating quantitatively the differences of pressure, we must see how they are ascertained for the arteries and veins. The method of obtaining the capillary pressure has been referred to already. If, in the neck of a mammal, the left common carotid artery be clamped in two places, it can, without loss of blood, be divided between the clamps, and a long straight glass tube, open at both ends, and of small calibre, can be tied into that stump of the artery which is still connected with the aorta, and which is called the "proximal" stump. If now the glass tube be held upright, and the clamp be taken off which has hitherto closed the artery between the tube and the aorta, the blood will mount in the tube, which is open at the top, to a considerable height, and will remain there. The external jugular vein of the other side should have been treated in the same way, but its tube should have been inserted into the "distal" stump—that is, the stump connected with the veins of the head, and not with the subclavian veins. If the clamp between the tube and the head have been removed at nearly the same time with that upon the artery, the blood may have mounted in the upright venous tube also, but only to a small distance. To cite an actual case in illustration, in a small etherized dog the arterial blood-column has been seen to stand at a height of about 155 centimeters above the level of the aorta, the height of the venous column about 18 centimeters above the same level. The heights of the arterial and venous columns of blood measure the pressures obtaining within the aorta and the veins of the head respectively, while at the same time the circulation continues to be free through both the aorta and the venous network. Therefore, in the dog above referred to, the aortic pressure was between eight and nine

[1] N. v. Kries: "Ueber den Druck in den Blutcapillaren der menschlichen Haut," *Berichte über die Verhandlungen der k. sächsischen Gesellschaft der Wissenschaften zu Leipzig,* math.-physische Classe, 1875, p. 149.

times as great as that in the smaller veins of the head. As, during such an experiment, the blood is free to pass from the aorta through one carotid and both vertebral arteries to the head, and to return through all the veins of that part, except one external jugular, to the vena cava, it is demonstrated that there must be a continuous flow from the aorta, through the capillaries of the head, into the veins, because the pressure in the aorta is many times as great as the pressure in the veins. Obviously, such an experiment, although very instructive, gives only roughly qualitative results.

Two things will be noted, moreover, in such an experiment. One is that the venous column is steady; the other is that the arterial column is perpetually fluctuating in a rhythmic manner. The top of the arterial column shows a regular rise and fall of perhaps a few centimeters, the rhythm of which is the same as that of the breathing of the animal; and, while the surface is thus rising and falling, it is also the seat of frequent flickering fluctuations of smaller extent, the rhythm of which is regular, and agrees with that of the heart's beat. At no time, however, do the respiratory fluctuations of the arterial column amount to more than a fraction of its mean height; compared to which last, again, the cardiac fluctuations are still smaller. It is clear, then, that the aortic pressure changes with the movements of the chest, and with the systoles and diastoles of the left ventricle. But stress is laid at present upon the fact that the aortic pressure at its lowest is several times as high as the pressure in the smaller veins of the head. Therefore, the occurrence of incessant fluctuations in the aortic pressure cannot prevent the continuous movement of the blood out of the arteries, through the capillaries, into the veins.

The upright tubes employed in the foregoing experiment are called "manometers."[1] They were first applied to the measurement of the arterial and venous blood-pressures by a clergyman of the Church of England, Stephen Hales, rector of Farringdon in Hampshire, who experimented with them upon the horse first, and afterward upon other mammals. He published his method and results in 1733.[2] The height of the manometric column is a true measure of the pressure which sustains it; for the force derived from gravity with which the blood in the tube presses downward at its lower opening is exactly equal to the force with which the blood in the artery or vein is pressed upward at the same opening. The downward force exerted by the column of blood varies directly with the height of the column, but, by the laws of fluid pressure, does not vary with the calibre of the manometer, which calibre may therefore be settled on other grounds. It follows also that the arterial and venous manometers need not be of the same calibre. Were, however, another fluid than the blood itself used in the manometer to measure a given intravascular pressure, as is easily possible, the height of the column would differ from that of the column of blood. For a given pressure the height

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[1] From μανός, rare. The name was given from such tubes being used to measure the tension of gases.

[2] Stephen Hales: *Statical Essays: containing Hæmastaticks*, etc., London, 1733, vol. ii. p. 1.

of the column is inverse to the density of the manometric fluid. For example, a given pressure will sustain a far taller column of blood than of mercury.

The Mercurial Manometer.— The method of Hales, in its original simplicity, is valuable from that very simplicity for demonstration, but not for research. The clotting of the blood soon ends the experiment, and, while it continues, the tallness of the tube required for the artery, and the height of the column of blood, are very inconvenient. It is essential to understand next the principles of the more exact instruments employed in the modern laboratory.

In 1828 the French physician and physiologist J. L. M. Poiseuille devised means both of keeping the blood from clotting in the tubes, and of using as a measuring fluid the heavy mercury instead of the much lighter blood. He thereby secured a long observation, a low column, and a manageable manometer.[1] The "mercurial manometer" of to-day is that of Poiseuille, though modified (see Fig. 100). In an improved form it consists of a glass tube open at both ends, and bent upon itself to the shape of the letter U. This is held upright by an iron frame. If mercury be poured into one branch of the U, it will fill both branches to an equal height. If fluid be driven down upon the mercury in one branch or "limb" of the tube, it will drive some of the mercury out of that limb into the other, and the two surfaces of the mercury may come to rest at very unequal levels. The difference of level, expressed in millimeters,
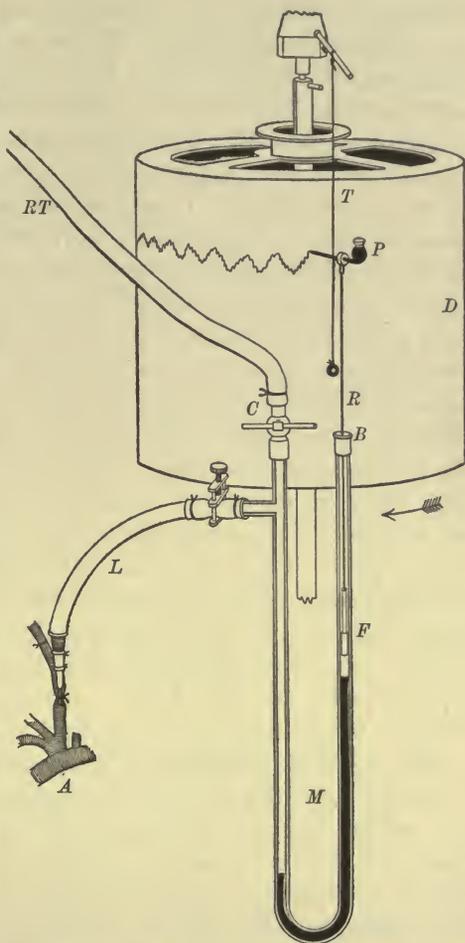
FIG. 100.—Diagram of the recording mercurial manometer and the kymograph; the mercury is indicated in deep black: *M*, the manometer, connected by the leaden pipe, *L*, with a glass cannula tied into the proximal stump of the left common carotid artery of a dog; *A*, the aorta; *C*, the stop-cock, by opening which the manometer may be made to communicate through *RT*, the rubber tube, with a pressure-bottle of solution of sodium carbonate; *F*, the float of ivory and hard rubber; *R*, the light steel rod, kept perpendicular by *B*, the steel bearing; *P*, the glass capillary pen charged with quickly drying ink; *T*, a thread which is caused, by the weight of a light ring of metal suspended from it, to press the pen obliquely and gently against the paper with which is covered *D*, the brass "drum" of the kymograph, which drum revolves in the direction of the arrow. The supports of the manometer and the body and clock-work of the kymograph are omitted for the sake of simplicity. The aorta and its branches are drawn disproportionately large for the sake of clearness.

[1] J. L. M. Poiseuille: *Recherches sur la force du cœur aortique*, Paris, 1828.

measures the height of the manometric column of mercury the downward pressure of which in one limb of the tube is just equal to the downward pressure of the fluid in the other. In order to adapt this "U-tube" to the study of the blood-pressure, that limb of the tube which is to communicate with the artery or vein is capped with a cock which can be closed. Into this same limb, a little way below the cock, opens at right angles a short straight glass tube, which is to communicate with the blood-vessel through a long flexible tube of lead, supported by the iron frame, and a short glass cannula tied into the blood-vessel itself. Two short pieces of india-rubber tube join the lead tube to the manometer and the cannula. Before the blood-vessel is connected with the manometer, the latter is filled with fluid between the surface of the mercury next the blood-vessel and the outer end of the lead tube, which fluid is such that when mixed with blood it prevents or greatly retards coagulation. With this same fluid the glass cannula in the blood-vessel is also filled, and then this cannula and the lead tube are connected. The cock at the upper end of the "proximal limb" of the manometer is to facilitate this filling, being connected by a rubber tube with a "pressure bottle," and is closed when the filling has been accomplished. The fluid introduced by Poiseuille and still generally used is a strong watery solution of sodium carbonate. A solution of magnesium sulphate is also good. If, in injecting this fluid, the column of mercury in the "distal limb" is brought to about the height which is expected to indicate the blood-pressure, but little blood will escape from the blood-vessel when the clamp is taken from it, and coagulation may not set in for a long time.

The Recording Mercurial Manometer and the Graphic Method.—When the arterial pressure is under observation, the combined respiratory and cardiac fluctuations of the mercurial column are so complex and frequent that it is very hard to read off their course accurately even with the help of a millimeter-scale placed beside the tube. In 1847 this difficulty led the German physiologist Carl Ludwig to convert the mercurial manometer into a self-registering instrument. This invention marked an epoch not merely in the investigation of the circulation, but in the whole science of physiology, by beginning the present "graphic method" of physiological work, which has led to an immense advance of knowledge in many departments. Ludwig devised the "recording manometer" by placing upon the mercury in the distal air-containing limb of Poiseuille's instrument an ivory float, bearing a light, stiff, vertical rod (see Fig. 100). Any fluctuation of the mercurial column caused float and rod to rise and fall like a piston. The rod projected well above the manometer, at the mouth of which a delicate bearing was provided to keep the motion of the rod vertical. A very delicate pen placed horizontally was fastened at right angles to the upper end of the rod. If a firm vertical surface, covered with paper, were now placed lightly in contact with the pen, a rise of the mercury would cause a corresponding vertical line to be marked upon the paper, and a succeeding fall would cause the descending pen to inscribe a second line covering the first. If now the vertical surface were made to move past the pen at a uniform rate,

the successive up-and-down movements of the mercury would no longer be marked over and over again in the same place so as to produce a single vertical line. The space and time taken up by each fluctuation would be graphically recorded in the form of a curve, itself a portion of a continuous trace marked by the successive fluctuations; thus both the respiratory and cardiac fluctuations could be registered throughout an observation by a single complex curving line. Ludwig stretched his paper around a vertical hollow cylinder of brass, made to revolve at a regular known rate by means of clock-work, and the conditions above indicated were satisfied[1] (see Fig. 100). Upon the surface of such a cylinder vertical distance represents space, and a vertical line of measurement is called, by an application of the language of mathematics, an " ordinate ; " horizontal distance represents time, and a horizontal line of measurement is called an " abscissa." The curve marked by the events recorded is always a mixed record of space and time. The instrument itself, the essential part of which is the regularly revolving cylinder, is called the " kymograph." [2] It has undergone many changes, and many varieties of it are in use. Any motor may be used to drive the cylinder, provided that the speed of the latter be uniform and suitable.

The curve written by the manometer or other recording instrument may either be marked upon paper with ink, as in Ludwig's earliest work ; or may be marked with a needle or some other fine pointed thing upon paper black-
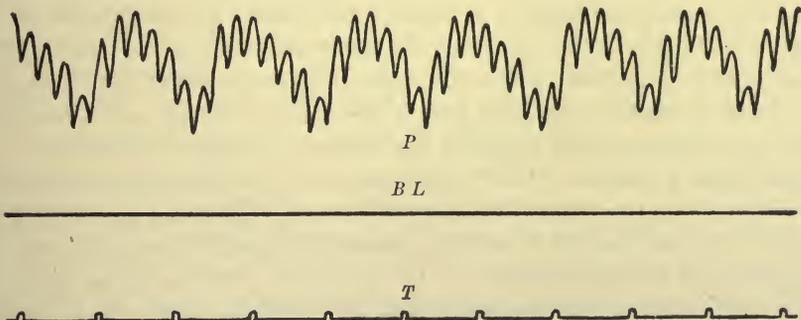
Fig. 101.—The trace of arterial blood-pressure from a dog anæsthetized with morphia and ether. The cannula was in the proximal stump of the common carotid artery. The curve is to be read from left to right.

P, the pressure-trace written by the recording mercurial manometer ;

B L, the base-line or abscissa, representing the pressure of the atmosphere. The distance between the base-line and the pressure-curve varies, in the original trace, between 62 and 77 millimeters, therefore the pressure varies between 124 and 154 millimeters of mercury, less a small correction for the weight of the sodium-carbonate solution ;

T, the time-trace, made up of intervals of two seconds each, and written by an electro-magnetic chronograph.

ened with soot over a flame. The trace written upon smoked paper is the more delicate. After the trace has been written, the smoked paper is removed from the kymograph and passed through a pan of shellac varnish. This

[1] C. Ludwig: "Beiträge zur Kenntniss des Einflusses der Respirationsbewegungen auf den Blutlauf im Aortensysteme," *Müller's Archiv für Anatomie, Physiologie, und wissenschaftliche Medicin*, etc., 1847, p. 242. [2] From κῦμα, a wave.

when dry fixes the trace, which thereafter will not be spoiled by handling. In Figure 101 the uppermost line shows a trace which fairly represents the successive fluctuations of the aortic pressure of the dog. The longer and ampler fluctuations are respiratory, the briefer and slighter are cardiac. In each respiratory curve the lowest point and the succeeding ascent coincide with inspiration; the highest point and the succeeding descent with expiration. The horizontal middle line is the base line, representing the pressure of the atmosphere. The base-line has been shifted upward in the figure simply in order to save room on the page. In the lowermost line the successive spaces from left to right of the reader represent successive intervals of time of two seconds each, written by an electro-magnetic chronograph. The pressure-trace taken from a vein may in certain regions near the chest show respiratory fluctuations, but nowhere cardiac ones, as the pulse is not transmitted to the veins. The venous pressure is so small, that for the practical study of it a recording manometer must be used in which some lighter fluid replaces the mercury, which would give a column of insufficient height for working purposes. The values obtained are then reduced by calculation to millimeters of mercury, for comparison with the arterial pressure. The intravascular pressure at a given moment can be measured by measuring a vertical line or "ordinate" drawn from the curve written by the manometer to the horizontal base-line. The latter represents the height of the manometric column when just disconnected from the blood-vessel; that is, when acted upon only by the weight of the atmosphere and of the solution of sodium carbonate. To ascertain the blood-pressure, the length of the line thus measured must be doubled; because the mercury in the proximal limb of the manometer sinks under the blood-pressure exactly as much as the float rises in the distal limb. A small correction must also be made for the weight of the solution of sodium carbonate.

The Mean Pressure.—The "mean pressure" is the average pressure during whatever length of time the observer chooses. The mean pressure for the given time is ascertained from the manometric trace by measurements too complicated to be explained here. As the weight and consequent inertia of the mercury cause it to fluctuate according to circumstances more or less than the pressure, the mean pressure is much more accurately obtained from the mercurial manometer than is the true height of each fluctuation, which is very commonly written too small. Therefore, it is especially the mean pressure that is studied by means of the mercurial manometer. The true extent and finer characters of the single fluctuations caused by the heart's beat are better studied with other instruments, as we shall see in dealing with the pulse.

It has been seen that the blood flows continuously through the capillaries because the pressure is continually high in the arteries and low in the veins. The reader is now in position to understand statements of the blood-pressure expressed in millimeters of mercury. The mean aortic pressure in the dog is far from being always the same even in the same animal. We have found it, in the case referred to on page 377, to be equivalent to about 121 millimeters of mercury. It will very commonly be found higher than this, and may range

up to, or above, 200 millimeters. In man it is probably higher than in the dog. The pressure in the other arteries derived from the aorta which have been studied manometrically is not very greatly lower than in that vessel. In the pulmonary arteries the pressure is probably much lower than in the aortic system. The pressure in the small veins of the head of the dog, the cannula being in the distal stump of the external jugular vein, we have found already in one case to equal about 14 millimeters of mercury. In such a case the presence of valves in the veins and other elements of difficulty make the mean pressure hard to obtain as opposed to the maximum pressure during the period of observation.

If a cannula be so inserted as to transmit the pressure obtaining within the great veins of the neck just at the entrance of the chest, without interfering with the movement of the blood through them, and if a manometer be connected with this cannula, the fluid will fall below the zero-point in the distal limb, indicating a slight suction from within the vein, and thus a slightly "negative" pressure.[1] This negative pressure may sometimes become more pronounced during inspiration and regain its former value during expiration. Sometimes, again, the pressure during expiration may become positive. The continuous flow from the great arteries through the capillaries to the veins, and through these to the auricle, is therefore shown by careful quantitative methods, no less than by the tube of Hales, to be simply a case of movement of a fluid from seats of high to seats of lower pressure.

The Symptoms of Bleeding in Relation to Blood-pressure.—The differences of pressure revealed scientifically by the manometer exhibit themselves in a very important practical way when blood-vessels are wounded and bleeding occurs. If an artery be cleanly cut, the high pressure within drives out the blood in a long jet, the length of which varies rhythmically with the cardiac pulse, but varies only to a moderate degree. From wounded capillaries, or from a wounded vein, owing to the low pressure, the blood does not spring in a jet, but simply flows out over the surface and drips away without pulsation. At the root of the neck, where the venous pressure may rhythmically fall below and rise above the atmospheric pressure, the bleeding from a wounded vein may be intermittent.

D. THE CAUSES OF THE PRESSURE IN THE ARTERIES, CAPILLARIES, AND VEINS.

The causes of the continuous high pressure in the arteries must first engage our attention.

Resistance.—The great ramification of the arterial system at a distance from the heart culminates in the formation of the countless arterioles on the confines of the capillary system. We have already seen direct evidence of the friction in the minute vessels which results from this enormous subdivision of the blood-path. The force resulting from this friction is propagated back-

[1] H. Jacobson: "Ueber die Blutbewegung in den Venen," *Reichert's und du Bois-Reymond's Archiv für Anatomie, Physiologie*, etc., 1867, p. 224.

ward according to the laws of fluid pressure, and constitutes a strong resist-
ance to the onward movement of the blood out of the heart itself.   Friction
is everywhere present in the vessels, but is greatest in the very small ones
collectively.

Power.—Where the aorta springs from the heart, the rhythmic contrac-
tions of the left ventricle force open the arterial valve, and force intermittent
charges of blood into the arterial system, overcoming thus the opposing force
derived from friction.   The wall of the arterial system is very elastic every-
where.   Thus the high pressure in the arteries results from the interaction of
the power derived from the heart's beat and the resistance derived from fric-
tion.   That the high pressure is continuous depends upon the capacity for
distention possessed by the elastic arterial wall.

Balance of the Factors of the Arterial Pressure.—In order to
study the causation of the arterial pressure, let us imagine that it has for some
reason sunk very low; but that, at the moment of observation, a normally
beating heart is injecting a normal blood-charge into the aorta.   The first
injection would find the resistance of friction present, and the elastic arterial
wall but little distended.   For this injection some room would be made by
the displacement of blood into the capillaries.   But it would be easier for the
arterial wall to yield than for the friction to be overcome, so the injected
blood would largely be stored within the arterial system and thus raise the
pressure.   Succeeding injections would have similar results; it would continue
to be easier for the injected blood to distend the arteries than to escape from
them; and the arterial pressure would rise rapidly toward its normal height.
Presently, however, a limit would be reached; a time would come when the
elastic wall, already well stretched, would have become tenser and stiffer and
would yield less readily before the entering blood; and now a larger part
than before of each successive charge of blood would be accommodated
by the displacement of an equivalent quantity into the capillaries, and a smaller
part by the yielding of the arterial wall.   Normal conditions of pressure
would be reached and maintained when the blood accommodated, during each
systole of the ventricle, by the yielding of the arterial wall should exactly
equal in amount the blood discharged from the arteries into the capillaries
during each ventricular diastole; for then the quantity of blood parted with
by the arteries during both the systole and the diastole of the heart would
be exactly the same as that received during its systole alone.

We see that, at each cardiac systole, the cardiac muscle does work in main-
taining the capillary flow against friction, and also does work upon the arte-
rial wall in expanding it.   A portion of the manifest energy of the heart's
beat thus becomes potential in the stretched elastic fibres of the artery.   The
moment that the work of expansion ceases, the stretched elastic fibres recoil;
their potential energy, just received from the heart, becomes manifest, and
work is done in maintaining the capillary flow against friction during the
repose of the cardiac muscle.   At the beginning of this repose the arterial
valves have been closed by the arterial recoil.   When, at each cardiac systole,

the arterial wall expands before the entering blood, the pressure rises, for more blood is entering the arterial system than is leaving it; when, at each cardiac diastole, the arterial wall recoils, the pressure falls, for blood is leaving the arterial system, and none is entering it. But before the fall has had time to become pronounced, while the arterial pressure is still high, the cardiac systole recurs, and the pressure rises again, as at the preceding fluctuation.

The Arterial Pulse.—The increased arterial pressure and amplitude at the cardiac systole, followed by diminished pressure and amplitude at the cardiac diastole, constitute the main phenomena of the arterial pulse. They are marked in the manometric trace by those lesser rhythmic fluctuations of the mercury which correspond with the heart-beats. The causes of the arterial pulse have just been indicated in dealing with the causes of the arterial pressure. The pulse, in some of its details, will be studied further for itself in a later chapter. For the sake of simplicity, the respiratory fluctuations of the arterial pressure have not been dealt with in the discussion just concluded. The causes of these important fluctuations are very complex and are treated of under the head of Respiration.

The arterial pressure, then, results from the volume and frequency of the injections of blood made by the heart's contraction; from the friction in the vessels; and from the elasticity of the arterial wall.

The Capillary Pressure and its Causes.—When we studied the movement of the blood in the capillaries, we found the pressure in them to be low and free from rhythmic fluctuations. In both of these qualities the capillary pressure is in sharp contrast with the arterial. What is the reason of the difference? The work of driving the blood through as well as into the capillaries is done during the contraction of the heart's wall by its kinetic energy. During the repose of the heart's wall and the arterial recoil this work is continued by kinetic energy derived, as we have seen, from the preceding cardiac contraction. The work of producing the capillary flow is done in overcoming the resistance of friction. The capillary walls are elastic. The same three factors, then—the power of the heart, the resistance of friction, the elasticity of the wall—which produce the arterial pressure produce the capillary pressure also. Why is the capillary pressure normally low and pulseless? The answer is not difficult. The friction which must be overcome in order to propel the blood out of the capillaries into the wider venous branches is only a part of the total friction which opposes the admission of the blood to the minuter vessels. The resistance is therefore diminished which the blood has yet to encounter after it has actually entered the capillaries. The force which propels the blood through the capillaries, although amply sufficient, is greatly less than the force which propels it into and through the larger arteries. In both cases alike the force is that of the heart's beat. But, in overcoming the friction which resists the entrance of the blood into the capillaries, a large amount of the kinetic energy derived from the heart has become converted into heat. The power is therefore diminished. As, in producing the high arterial pressure, much power is met by much resistance, and the elastic wall

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is, therefore, distended with accumulated blood; so, in producing the low capillary pressure, diminished power is met by diminished resistance, outflow is relatively easy, accumulation is slight, and the elasticity of the delicate wall is but little called upon.

The Extinction of the Arterial Pulse.—But why is the capillary pressure pulseless, as the microscope shows? To explain this, no new factors need discussion, but only the adjustment of the arterial elasticity to the intermittent injections from the heart and to the total friction which opposes the admission of blood to the capillaries. This adjustment is such that the recoil of the arteries displaces blood into the capillaries during the ventricular diastole at exactly the same rate as that produced by the ventricular contraction during the ventricular systole. Thus, through the elasticity of the arteries, the cardiac pulse undergoes extinction; and this becomes complete at the confines of the capillaries. The respiratory fluctuations become extinguished also, and the movement of the blood in the capillaries exhibits no rhythmic changes. This conversion of an intermittent flow into one not merely continuous but approximately constant affords a constant blood-supply to the tissues, at the same time that the cardiac muscle can have its diastolic repose, and the ventricular cavities the necessary opportunities to receive from the veins the blood which is to be transferred to the arteries.

A simple experiment will illustrate the foregoing. Let a long india-rubber tube be taken, the wall of which is thin and very elastic. Tie into one end of the tube a short bit of glass tubing ending in a fine nozzle, the friction at which will cause great resistance to any outflow through it. Tie into the other end of the rubber tube an ordinary syringe-bulb of india-rubber, with valves. Expel the air, and inject water into the tube from the valved bulb by alternately squeezing the latter and allowing it to expand and be filled from a basin. The rubber tube will swell and pulsate, but if its elasticity have the right relation to the size of the fine glass nozzle and to the amplitude and frequency of the strokes of the syringe, a continuous and uniform jet will be delivered from the nozzle, while the injections of water will, of course, be intermittent.

The Venous Pressure and its Causes.—The pressure in the peripheral veins is less than in the capillaries and declines as the blood reaches the larger veins. Very close to the chest the pressure is below the pressure of the atmosphere, and may sometimes vary from negative to positive, following the rhythm of the breathing. These respiratory fluctuations will be considered later. The low and declining pressures under which the blood moves through the venules and the larger veins are due to the same causes as those which account for the capillary pressure. It is still the force generated by the heart's contractions, and made uniform by the elastic arteries, which drives the blood into and through the veins back to the very heart itself. As the blood moves through the veins, what resistance it encounters is still that of the friction ahead. But the friction ahead is progressively less; the conversion of kinetic energy into heat is progressively greater. The venous wall possesses elas-

ticity, but this is even less called upon than that of the capillaries; and, presently, in the larger veins, the moving blood is found to press no harder from within than the atmosphere from without.

Subsidiary Forces which Assist the Flow in the Veins.—There are certain forces which, occasionally or regularly, assist the heart to return the venous blood into itself. Too much stress is often laid upon these; for it is easy to see by experiment that the heart can maintain the circulation wholly without help. The origins of these subsidiary forces are, first, the contraction of the skeletal muscles in general; second, the continuous traction of the lungs; third, the contraction of the muscles of inspiration.

The Skeletal Muscles and the Venous Valves.—A vein may lie in such relation to a muscle that when the latter contracts the vein is pressed upon, its feeble blood-pressure is overborne, the vein is narrowed, and blood is squeezed out of it. The veins in many parts are rich in valves, competent to prevent regurgitation of the blood while permitting its flow in the physiological direction. The pressure of a contracting muscle, therefore, can only squeeze blood out of a vein toward the heart, never in the reverse direction. Muscular contraction, then, may, and often does, assist in the return of the venous blood with a force not even indirectly derived from the heart. But such assistance, although it may be vigorous and at times important, is transient and irregular. Indeed, were a given muscle to remain long in contraction, the continued squeezing of the vein would be an obstruction to the flow through it.

The Continuous Pull of the Elastic Lungs.—The influence of thoracic aspiration upon the movement of the blood in the veins deserves a fuller discussion. The root of the neck is the region where this influence shows itself most clearly, but it may also be verified in the ascending vena cava of an animal in which the abdomen has been opened. The physiology of respiration shows that not only in inspiration, but also in expiration, the elastic fibres of the lungs are upon the stretch, and are pulling upon the ribs and intercostal spaces, upon the diaphragm, and upon the heart and the great vessels. This dilating force at all times exerted upon the heart by the lungs is of assistance, as we shall see, in the diastolic expansion of its ventricles. In the same way the elastic pull of the lungs acts upon the venæ cavæ within the chest, and generates within them, as well as within the right auricle, a force of suction. The effects upon the venous flow of this continuous aspiration are best known in the system of the ascending vena cava. This suction from within the chest extends to the great veins just without it in the neck. In these, close to the chest, as we have seen, manometric observation reveals a continuous slightly negative pressure. A little farther from the chest, however, but still within the lower portions of the neck, the intravenous pressure is slightly positive. The elastic pull of the lung, therefore, continuously assists in unloading the terminal part of the venous system, and thus differs markedly from the irregular contractions of the skeletal muscles.

The Contraction of the Muscles of Inspiration.—But some skeletal

muscles, those of inspiration, regularly add their rhythmic contractions to the continuous pull of the lungs, to reinforce the latter. Each time that the chest expands there is an increased tendency for blood to be sucked into it through the veins. At the beginning of each expiration this increase of suction abruptly ceases.

The Respiratory Pulse in the Veins near the Chest, and its Limitation.—In quiet breathing the movements of the chest-wall produce no very conspicuous effect. If, however, deep and infrequent breaths be taken, the pressure within the veins close to the chest becomes at each inspiration much more negative than before; and at each inspiration the area of negative pressure may extend to a greater distance from the chest along the veins of the neck, and perhaps of the axilla. As the venous pressure in these parts now falls as the chest rises, and rises as the chest falls, a visible venous pulse presents itself, coinciding, not with the heart-beats, but with the breathing. At each inspiration the veins diminish in size, as their contents are sucked into the chest faster than they are renewed. At each expiration the veins may be seen to swell under the pressure of the blood coming from the periphery. If the movements of the air in the windpipe be mechanically impeded, these changes in the veins reach their highest pitch; for then the muscles of expiration may actually compress the air within the lungs, and produce a positive pressure within the vena cava and its branches, with resistance to the return of venous blood during expiration, shown by the exaggerated swelling of the veins. These phenomena are suddenly succeeded by suction, and by collapse and disappearance of the veins from view, as inspiration suddenly recurs. The respiratory venous pulse, when it occurs, diminishes progressively and rapidly as the veins are observed farther and farther from the root of the neck,—a fact which results from the flaccidity of the venous wall. Were the walls of the veins rigid, like glass, the successive inspirations would produce rhythmic accelerations of the flow throughout the whole venous system, and the contractions of the muscles of inspiration would rank higher than they do among the causes of the circulation. In fact, the walls of the veins are very soft and thin. If, therefore, near the chest, the pressure of the blood within the veins sink below that of the atmosphere without, the place of the blood sucked into the chest is filled only partly by a heightened flow of blood from the periphery, but partly also by the soft venous wall, which promptly sinks under the atmospheric pressure. This is shown by the visible flattening, perhaps disappearance from view, of the vein. This process reduces the venous pulse, where it occurs, to a local phenomenon; for, at each inspiration, the promptly resulting shrinkage of all the affected veins together is just equivalent to the loss of volume due to the sucking of blood into the chest. Therefore the flow in the more peripheral veins remains unaffected, and the pressure within them continues to be pulseless and positive. During expiration the swelling of the veins near the chest, the return of positive pressure within them, may be simply from the return of the ordinary balance of forces after the effects of a deep inspiration have disappeared. But, if expiration be

violent and much impeded, the positive pressure may rise much above the normal. Here again, however, regurgitation will meet with opposition from the venous valves, though the flow from the periphery may be much impeded.

The "Dangerous Region," and the Entrance of Air into a Wounded Vein.—Quite close to the chest, then, the normal venous pressure is always slightly negative; and in deep inspiration it may become more so, and this condition may extend farther from the chest along the neck and axilla, throughout a region known to surgeons as "the dangerous region." It is important to understand the reason for this expression. It has already been mentioned that the wounding of a vein in this region may cause intermittent bleeding. It now will easily be understood that such bleeding will occur only when the pressure is positive—that is, during expiration. During deep and difficult breathing, indeed, the venous blood may spring in a jet during expiration instead of merely flowing out, and may wholly cease to flow during inspiration. The cessation is due, of course, to the blood being sucked into the chest past the wound rather than pressed out of it.

It is not, however, the risks of hemorrhage that have earned the name of "dangerous" for the region where intermittent bleeding may occur. The danger referred to is of the entrance of air into the wounded vein and into the heart,—an accident which is commonly followed by immediate death, for reasons not here to be discussed. Very close to the chest, where the venous pressure is continuously negative and the veins are so bound to the fasciæ that they may not collapse, this danger is always present. Throughout the rest of the dangerous region, the entrance of air into a wounded vein will take place only exceptionally. In quiet breathing the venous pressure is continuously positive throughout most of this region; and then a wounded vein will merely bleed. It is only in deep breathing that a venous pulse becomes visible here, and that the venous pressure becomes negative in inspiration. But even in forced breathing it is rare for a wounded vein of the dangerous region to do more than bleed. The cause of this lies in the flaccidity of the venous wall. At each expiration the blood may jet from the wound; but at the following deep inspiration the weight of the atmosphere flattens the vein so promptly that the blood is followed down by the wounded wall and no air enters at the opening. It is only when, during deep breathing, the wounded wall for some reason cannot collapse, that the main part of the "dangerous region" justifies its name. Should the tissues through which the vein runs have been stiffened by disease, or should the wall of the vein adhere to a tumor which a surgeon is lifting as he cuts beneath it, in either case the vein will have become practically a rigid tube. Should it be wounded during a deep inspiration, blood will be sucked past the wound, but the atmospheric pressure will fail to make the wall collapse; air will be drawn into the cut, and blood and air will enter the heart together, probably with deadly effect.

Summary.—It appears from what has gone before that the elasticity of the lungs and the contractions of the muscles of inspiration regularly assist in

unloading the veins in the immediate neighborhood of the heart, and so remove some part of the resistance to be overcome by the contractions of the cardiac muscle. When we come to the detailed study of the heart it will appear also that a slight force of suction is generated by the heart itself, which force adds its effects upon the flow of venous blood to those of the elasticity of the lungs and of the contraction of the muscles of inspiration.

It must here be repeated, however, that the heart is quite competent to maintain the circulation unaided. This is proven as follows: If in an anæsthetized mammal a cannula be placed in the windpipe, the chest be widely opened, and artificial respiration be established, the circulation, though modified, continues to be effective. By the opening of the chest its aspiration has been ended, and can, no longer assist in the venous return. If, further, the animal be drugged in such a manner as completely to paralyze the skeletal muscles throughout the body, their contractions can exert no influence upon the venous return; yet the circulation is still kept up by the heart, unaided either by the elasticity of the lungs, by the contractions of the muscles which produce inspiration, or by those of any other skeletal muscles.

E. The Speed of the Blood in the Arteries, Capillaries, and Veins.

If we keep as our text, in discussing the circulation, the character of the capillary flow, it will be seen that we have now accounted for the facts that the capillary flow is toward the veins; that it shows much friction; that it is continuous, pulseless, and under low pressure. We have not yet accounted for the fact that it is slow. We must now do so, but must first state and account for the speed of the blood in the arteries and veins.

The Measurement of the Blood-speed in Large Vessels; the "Stromuhr."—The speed of the blood in the larger veins and arteries must be measured indirectly. We can picture to ourselves the volume of blood which moves past a given point in a given blood-vessel in one second, as a cylinder of blood having the same diameter as the interior of the blood-vessel. The length of this cylinder will then be expressed by the same number which will express the velocity with which a particle of the blood would pass the given point in one second, provided that this velocity be uniform and be the same for all the particles. In order, then, to learn the average speed of the blood at a given point of an artery or vein during a certain number of seconds, we have only to measure the calibre of the blood-vessel and the quantity of blood which passes the selected point during the period of observation. From these two measurements the speed can be obtained by calculation. But these two measurements are not quite easy. The physical properties of the blood-vessels, especially of the veins, make their calibres variable and hard to estimate justly as affected by the conditions present during an experiment. The means adopted for measuring the quantity of blood passing a point in a given time necessarily alters the resistance encountered by the flow, and so of itself affects both the rate of flow and the blood-pressure; and, with the

latter, the calibre of the vessel. For these reasons any measurement of the average speed of the blood by the above method is only approximately correct. The best instrument for measuring the quantity of blood driven past a point during an experiment is the so-called "strom-uhr" or "rheometer" of Ludwig, a longitu-dinal section of which is given diagrammati-cally in Figure 102.[1] This is essentially a curved tube shaped like the Greek capital letter Ω. Each end of the tube is tied into one of the two stumps (*a* and *b*) of the divided vessel. These ends of the tube are as nearly as possible of the same calibre as the vessel selected. Each limb of the tube is dilated into a bulb, and the upper part of the tube, including the two bulbs, is of glass; the lower part of each limb is of metal. At the top, between the bulbs, is an opening for filling the tubes, which can easily be closed when not in use. Each end of the tube is filled with defibrinated blood before being tied into the blood-vessel. In the limb of the tube (*B*,

FIG. 102.—Diagram of longitudinal sec-tion of Ludwig's "Stromuhr." The ar-rows mark the direction of the blood-stream. For further description see the text.

Fig. 102) which is the farther from the heart if an artery be used, or the nearer to the heart if a vein, the defibrinated blood is made to fill the cavity up to the top of the bulb. In the other limb (*A*, Fig. 102) the blood fills the tube only up to a mark (*e*, Fig. 102) near the bottom of the bulb. Through the opening between the bulbs the still vacant space, which includes the whole of the bulb *A*, is filled with oil, all air being excluded. The opening is then closed. If now the clamps be removed from the blood-vessel, the blood of the animal will enter the tube at *a* and drive before it the contents of the tube. Thus defibrinated blood from *B* will be driven into the distal stump of the vessel at *b*, and will enter the circulation of the animal. Oil will at the same time be driven over from *A* to *B*. The bulb *A* has upon it two marks, *d* and *e*, one near the top of it, the other near the bottom. The instant when the line between the oil and the advancing blood reaches the mark near the top of *A* is the instant when a volume of blood equal to that of the displaced oil has entered *A*, past the mark near the bottom of it. The capacity of the tube between the two marks is accurately known. The time required for this space to be filled with the entering blood is measured by the observer. The calibre of the metal tube at *a* is accurately known, and is assumed to be equal to the calibre of the blood-vessel. From these measurements the average speed of the blood-stream at *a* is calculated.

[1] J. Dogiel: "Die Ausmessung der strömenden Blutvolumina," *Berichte über die Verhand-lungen der k. sächsischen Gesellschaft der Wissenschaften zu Leipzig, Math.-physische Classe*, 1867, p. 200.

The metallic lower part of the instrument, which includes both limbs of the tube, is completely divided horizontally at *c.* The two parts are so built, however, as to be maintained in water-tight apposition. This arrangement permits the whole upper part of the instrument, including the glass bulbs, to be rotated suddenly upon the lower, so that the bulb *B* may correspond with the entrance for the blood at *a*, and the bulb *A* with the exit for the blood at *b.* If this rotation be effected at the instant when the space between the two marks on *A* has been filled with blood, the bulb *B*, now charged with oil, will be filled by the blood which enters next, and the first charge of the animal's own blood will make its exit at *b.* Oil will now pass over from *B* to *A ;* when the line between it and the blood which is leaving *A* has just reached the lower mark on *A*, the bulbs are turned back to their original position. Thus, by repeated rotations, each of which can be made to record upon the kymograph the instant of its occurrence, a number of charges of blood can be received and transmitted in succession ; it is always the same space, between the marks on *A*, which is used for measuring the charge ; and the time of the experiment can be much prolonged. By this procedure the errors due to a single brief observation can be greatly reduced. Indeed, the time of entrance of a single charge of blood would be quite too short to give a satisfactory result.

The use of the stromuhr not only affords necessary data for the calculation of the average speed of the blood, but seeks directly to measure the volume of blood delivered in a given time by an artery to its capillary district. It is evident that this volume is a quantity of fundamental importance in the physiology of the circulation. Could we ascertain it, by direct measurement or by calculation, for the aorta or pulmonary artery, we should know at once the volume of blood delivered to the capillaries in one second, and thus the time taken for the entire blood to enter either those of the lungs or of the system at large. By this knowledge, many important problems would be advanced toward solution.

The Measurement of Rapid Fluctuations of Speed.—The stromuhr can give only the average speed of the blood during the experiment. To study rapid fluctuations of speed, another method is needed. If, in a large animal, a vessel, best an artery, be laid bare, a needle may be thrust into it at right angles. If the needle be left to itself, the end which projects from the artery will be deflected toward the heart, because the point will have been deflected toward the capillaries by the blood-stream. The angle of deflection might be read off, could a graduated semicircle be adjusted to the needle. If the stream be arrested, the needle returns to its position at right angles to the artery. The greater the velocity of the stream, the greater is the deflection of the needle. If, later, the same needle be thrust into a tube of rubber through which water flows at known rates of speed, the speed corresponding to each angle of deflection of the needle may be determined. If the needle were made to mark upon a kymograph, variations of the speed would be recorded as a curve.

An instrument based on the principles just described is valuable for the study of rapid changes of velocity.[1] In an artery, its needle oscillates rhythmically, showing that there the speed of the blood varies during each beat of the heart, being greatly accelerated by the systole of the ventricle, and retarded by the cessation of the systole. It will be remembered that the microscope directly shows faint rhythmic accelerations in the minute arteries of the frog. In the veins rhythmic changes of speed do not occur except near the heart from respiratory causes.

The Speed of the Blood in the Arteries.—The stromuhr shows that the speed of the blood is liable to great variations. This fact, and the range of speed in the arteries, are fairly exhibited by the results obtained by Dogiel from the common carotid artery of a dog, the experiment upon which lasted 127 seconds. During this time six observations were made which varied in length from 14 to 30 seconds each. For one of these periods the average speed was 243 millimeters in one second; for another period, 520 millimeters. These were the extremes of speed noted in this case.[2] The speed in the arteries diminishes toward the capillaries.

The Speed of the Blood in the Veins.—The speed in a vein tends to be slower than that in an artery of about the same importance, but is not necessarily so.[3] It increases from the capillaries toward the heart.

The Speed of the Blood in the Capillaries.—The rate of the capillary flow may be measured directly under the microscope. Certain physiologists have also observed the movement of the blood in the retinal capillaries of their own eyes, and have measured its rate there.[4] Both methods show that in the capillaries the speed is very much less than in the large arteries or large veins. In the capillaries of the web of the frog's foot it is only about 0.5 millimeter in one second. In those of the mesentery of a young dog it has been found to be 0.8 millimeter; in those of the human retina, from 0.6 to 0.9 millimeter.

Speed and Pressure of the Blood Compared.—If now we compare the speed with the pressure of the blood in the arteries, in the capillaries, and in the veins, we shall be struck by both similarities and differences. In the arteries both pressure and speed rhythmically rise and fall together; and both the mean pressure and the mean speed decline from the heart to the capillaries. In the capillaries both pressure and speed are pulseless and low,—very low compared with the great arteries. In the veins, however, the pressure is everywhere lower than in the capillaries and falls from the capillaries to the heart; the speed is everywhere higher than in the capillaries and rises from

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[1] M. L. Lortet: *Recherches sur la vitesse du cours du sang dans les artères du cheval au moyen d'un nouvel hémodromographe*, Paris, 1867.

[2] J. Dogiel: *loc. cit.*

[3] E. Cyon und F. Steinmann: " Die Geschwindigkeit des Blutstroms in den Venen," *Bulletin de l'Académie Impériale des Sciences de St. Pétersbourg*, 1871; also in E. Cyon: *Gesammelte physiologische Arbeiten*, 1888, p. 110.

[4] K. Vierordt: *Die Erscheinungen und Gesetze der Stromgeschwindigkeiten des Blutes*, etc., 1862, pp. 41, 111.

the capillaries to the heart. It is apparent, therefore, that there is no direct connection between the pressure and the speed of the blood at a given point, inasmuch as they change together along the arteries and change inversely along the veins. How varied the combinations may be of pressure and speed will be seen in studying the regulation of the circulation.

In the great veins, as in the arteries, the speed is very high compared with the capillaries. In the capillaries the speed of the blood is least, while in the tubes which supply and which drain them the speed is great. The physiological value of these facts is clear. It has already been pointed out that the blood moves slowly through the short and narrow tubes, where its exchanges with tissue and with air are effected, and swiftly through the long tubes of communication. What are the physical conditions which underlie these physiological facts?

The speed of the blood varies inversely as the collective sectional area of its path. If the circulation in an animal continue uniform for a time —during several breaths and heart-beats—it is evident that the forces concerned must be so balanced that, during that time, equal quantities of blood will have entered and left the heart, the arteries, the capillaries, and the veins, respectively. If the arteries, for instance, lose more blood than the heart transmits to them, this blood must accumulate in the veins till the arteries become drained and the supply to the capillaries fails. The very maintenance of a circulation, then, implies that equal quantities of blood must pass any two points of the *collective* blood-path in equal times, except when a general readjustment of the rate of flow may lead to a temporary disturbance of it. It will be seen at once that this principle is consistent with the widest differences of rate between individual arteries of the same importance, or between individual veins or capillaries. If in one artery the flow be increased by one-half, and in another be diminished by one-half, the total flow in the two arteries collectively will be the same as before.

If the principle just stated be considered in connection with the anatomy of the blood-path, the differences of speed in the arterial, capillary, and venous systems will at once be understood. The wider arteries and veins are few. Dissection shows that when an artery or vein divides, the calibre, and, with the calibre, the "sectional area" of the branches taken together, is commonly larger than that of the parent trunk. In general it is a law of the arterial and venous anatomy that the collective sectional area of the vessels of either system increases from the heart to the capillaries. The smaller the individual vessels are, the wider is the blood-path which they make up collectively. Widest of all is the blood-path where the individual vessels are smallest—that is, in the capillary system. The collective sectional area of the capillaries is several hundred times that of the root of the aorta. The collective sectional area of the veins which enter the right auricle is greater, perhaps twice as great, as that of the root of the aorta. The venous system, regarded as a single tube, is of much greater calibre than the arterial. It is perhaps better to make these general statements than to compare the different figures given

by different observers. The arterial and venous systems, treated as each a single tube, may be compared roughly to two funnels, each having its narrow end at the heart. The very wide and very short single tube of the capillary system may be imagined to connect the wide ends of the two funnels. Equal quantities of blood pass in equal times any two points of the collective blood-path between the left ventricle and the right auricle. Therefore where the blood-path is wide, these quantities must move slowly, and swiftly where the blood-path is narrow. It is owing, then, to the rapid widening of the arterial path that the speed declines, like the pressure, toward the capillaries. It is owing to the huge relative calibre of the path at the capillaries that in them the speed is by far the least while the same volume is passing that passes a point in the narrow aorta in the same time; it is owing to the steady narrowing of the venous path toward the heart that the venous blood is constantly quickening its speed while its pressure is falling. As the calibre of the venous system is greater than that of the arterial, the average speed in the veins is probably less than in the arteries. As the collective calibre of the veins which enter the right auricle is greater than that of the aorta, the blood probably moves into the heart less swiftly than out of it; though of course equal quantities enter and leave it in equal times provided those times are not mere fractions of a beat. In connection with this it is significant that the entrance of blood into the heart takes place during the long auricular diastole, while its exit is limited to the shorter ventricular systole.

Time Spent by the Blood in a Systemic Capillary.—The width of the path, then, determines the slow movement of the blood in the areas where it is fulfilling its functions; the narrowness of the path, the swiftness of movement of the blood in leaving and returning to the heart. We have seen (p. 371) that a particle of blood may make the entire round of a dog's circulation in from fifteen to eighteen seconds. If we assume the systemic capillary flow to be at the rate of 0.8 millimeter in one second, the blood would remain about 0.6 of a second in a systemic capillary half a millimeter long. Slow as is the capillary flow, it thus appears that it is none too slow to give time for the uses of the blood to be fulfilled.

F. The Flow of Blood through the Lungs.

The blood moves from the right ventricle to the left auricle under the same general laws as from the left ventricle to the right auricle. Certain differences, however, are apparent, and must be noted. One difference is that the collective friction is less in the pulmonary than in the systemic vessels, and that therefore the resistance to be overcome by each contraction of the right ventricle is less than that opposed to the left ventricle. Accordingly it appears from dissection that the muscular wall of the right ventricle is much thinner than that of the left. No accurate measurements can be made of the normal pressure and speed of the blood in the arteries, capillaries, and veins of the lungs, because they can be reached only by opening the chest and destroying the mechanism of respiration, and thereby disturbing the normal

conditions of the pulmonary blood-stream. In the opened chest these cannot be entirely restored by artificial respiration. The thinness of the wall of the pulmonary artery, however, indicates that it has much less pressure to support than that of the aorta, which fact also is indicated by such roughly approximate results as have been obtained with the manometer after opening the chest.

As the pulmonary artery and veins lie wholly within the chest, but outside the lungs, their trunks and larger branches all tend to be dilated continuously by the elastic pull of the lungs—a pull which increases at each inspiration. On the other hand, the pulmonary capillaries lie so close to the surface of each lung that they are exposed to the same pressure, practically, as that surface, and the full weight of the atmosphere may act upon them. These conditions all tend to unload the capillaries and the pulmonary veins, but to weaken the unloading of the pulmonary artery. The two effects can hardly balance one another, however. The wall of the pulmonary artery is so much stiffer than that of the vein, that the actual results should be favorable to the flow. The elasticity of the lungs and the contractions of the muscles of inspiration thus lighten, probably, the work of the right ventricle as well as of the left. The right ventricle, however, like the left, can accomplish its work without assistance; for the entire circulation, including, of course, the flow through the lungs, continues after the chest has been opened, if artificial respiration be maintained.

G. The Pulse-volume and the Work done by the Ventricles of the Heart.

The Cardiac Cycle.—It is assumed that the anatomy of the heart is known to the reader.

The general nature and effects of the heart's beat have been sketched already. Each beat has been seen to comprise a number of phenomena, which occur in regular order, and which recur in the same order during each of the succeeding beats. Each beat is therefore a cycle; and the phrase " cardiac cycle " has become a technical expression for " beat," as it conveys, in a word, the idea of a regular order of events. As each of the four chambers of the heart has its own systole and diastole, there are eight events to be studied in connection with each cycle. The systoles of the two auricles, however, are exactly simultaneous, as are their diastoles; and the same is true of the systoles and of the diastoles of the two ventricles. We may, therefore, without confusion, speak of the auricular systole and diastole, and of the ventricular systole and diastole, as of four events, each involving the narrowing or widening of two chambers, a right and a left. The heart of the mammal or bird consists essentially of a pair of pumps, the ventricles, each of which acts alternately as a powerful force-pump and as a very feeble suction-pump. To each ventricle is superadded a contractile appendage, the auricle, through which, and to some extent by the agency of which, blood enters the ventricle.

The Pulse-volume.—The central fact of the circulation of the blood is the injection, at intervals, by each ventricle, against a strong resistance, of a charge of blood into its artery, which charge the ventricle has just received out of its veins through its auricle. This quantity must be exactly the same for the two ventricles under normal conditions, or the circulation would soon come to an end by the accumulation of the blood in either the pulmonary or the systemic vessels. The blood ejected from each ventricle during the systole must also be equal in volume to the blood which enters each set of capillaries, the pulmonary or systemic, during that systole and the succeeding diastole of the ventricles, provided the circulation be proceeding uniformly. The quantity just referred to is called the " contraction volume " or " pulse-volume " of the heart. Were it always the same, and could we measure it, we should possess the key to the quantitative study of the circulation.

The pulse-volume may vary in the same heart at different times, as is easily shown by opening the chest, causing the conditions of the circulation to change, and noting that under certain conditions the heart during each beat varies in size more than before. This variation of volume is easily possible because the walls of the heart are of muscle, soft and distensible when relaxed. It is probable that at no systole is the ventricle quite emptied; that most of its cavity may become obliterated by the coming together of its walls, but that a space remains, just below the valves and above the papillary muscles, which is not cleared of blood. It is also probable that not only the blood which is ejected at the systole may vary in amount, but also the residual blood which remains in the ventricle at the end of the systole.[1] It is therefore clear that it is useless to attempt the measurement of the pulse-volume by measuring the fluid needed to fill the ventricle, even if the heart be freshly excised from the living body and injected under the normal blood-pressure. Rough approximations to this measurement may, however, be attempted in at least two ways:

In the first place, a modification of the stromuhr has been applied successfully to the aorta of the rabbit, between the origins of the coronary arteries and of the innominate. This operation requires that the auricles be clamped temporarily so as to stop the flow of blood into the ventricles, and to permit the aorta in its turn to be clamped and divided between the clamp and the ventricle, without serious bleeding. After the circulation has been re-established, the volume of the blood which passes through the instrument during the experiment, divided by the number of the heart-beats during the same period, gives the pulse-volume. The average result obtained, for the rabbit,

[1] F. Hesse: "Beiträge zur Mechanik der Herzbewegung," *Archiv für Anatomie und Physiologie* (anatomische Abtheilung), 1880, p. 328. C. Sandborg und W. Müller : "Studien über den Mechanismus des Herzens," *Pflüger's Archiv für die gesammte Physiologie*, 1880, xxii. p. 408. C. S. Roy and J. G. Adami : "Contributions to the Physiology and Pathology of the Mammalian Heart," *Proceedings of the Royal Society of London*, 1891–92, i. p. 435. J. E. Johansson und R. Tigerstedt : "Ueber die gegenseitigen Beziehungen des Herzens und der Gefässe ;" "Ueber die Herzthätigkeit bei verschieden grossem Wiederstand in den Gefässen," *Skandinavisches Archiv für Physiologie*, 1891, ii. p. 409.

is a volume of blood the weight of which is 0.00027 of the weight of the animal.[1]

A second way of attempting to ascertain the pulse-volume is to measure the swelling and the shrinkage of the heart. This is called the "plethysmographic"[2] method. One application of it is as follows: The chest and pericardium of an animal are opened, and the heart is inserted into a brass case full of oil. The opening through which the great vessels pass is made water-tight by mechanical means which do not impede the movement of the blood into and out of the heart. The top of the brass case is prolonged into a tube, the oil in which rises as the heart swells and falls as it shrinks. Upon the oil a light piston moves up and down, and records its movements upon the kymograph. The instrument is called a "cardiometer."[3]

The average pulse-volume of the human ventricle has been very variously estimated upon the basis of observations of various kinds made upon mammals of various species. The figures offered range, in round numbers, from 50 to 190 cubic centimeters. If we assume the human pulse-volume to weigh 100 grams, and the blood of a man who weighs 69 kilograms to weigh 5.308 kilograms, or $\frac{1}{13}$ of his body-weight, the pulse-volume will be about $\frac{1}{53}$ of the entire blood, and the entire blood will pass through the heart, from the veins to the arteries, in only fifty-three beats—that is, in less than one minute. The speed with which a man may bleed to death if a great artery be severed is therefore not surprising.

The Work done by the Contracting Ventricles.—Uncertain as is this important quantity of the pulse-volume, the estimation of the work done by the heart in maintaining the circulation must be based upon it, and upon the force with which each ventricle ejects the pulse-volume. A small fraction of this force is expended in imparting a certain velocity to the ejected blood; all the rest serves to overcome a number of opposing forces. The force exerted by the muscular contraction is opposed by the weight of the volume ejected, and by the strong arterial pressure, which resists the opening of the semilunar valve and the ejection of the pulse-volume. Moreover, the elasticity of the lungs tends at all times to dilate the ventricles, with a force which is increased at each recurring contraction of the muscles of inspiration. Probably there is also in the wall of the ventricle itself a slight elasticity which must be overcome by the ventricle's own contraction in order that its cavity may be effaced. The strong arterial pressure, with which the reader is already familiar, is by far the greatest of these resisting forces—in fact, is the only one of them which is not of small importance in the present connection.

Are we obliged to measure the force of the systole indirectly? Can we not ascertain it by direct experiment? Manometers of various kinds have been placed in direct communication with the cavities of the ventricles. The fol-

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[1] R. Tigerstedt: "Studien über die Blutvertheilung im Körper." Erste Abhandlung. "Bestimmung der von dem linken Herzen herausgetriebenen Blutmenge," *Skandinavisches Archiv für Physiologie*, 1891, iii. p. 145.

[2] From πληθυσμός, enlargement.   [3] C. S. Roy and J. G. Adami, *op. cit.*

lowing method, among others, has been employed : A tube open at both ends is introduced through the external jugular vein of an animal into the right ventricle, or, with greater difficulty, through the carotid artery into the left ventricle. In neither case is the valve, whether tricuspid or aortic, rendered incompetent during this proceeding, nor need the general mechanism of the heart and vessels be gravely disturbed. If the outer end of the tube be connected with a recording mercurial manometer, a tracing of the pressure within the right or left ventricle may be written upon the kymograph. It is found, however, that the pressure within the heart varies so much and so rapidly that the inert mercurial column will not follow the fluctuations, and that the attempt to learn the mean pressure by this method fails. A valve, however, may be intercalated in the tube between the ventricle and the manometer—a valve so made as to admit fluid freely to the manometer, but to let none out. The manometer will then record, and record not too incorrectly, the maximum pressure within the right or left ventricle during the experiment ; in other words, it will record the greatest force exerted during that time by the ventricle in order to do its work.[1] In this way the maximum pressure within the left ventricle of the dog has been found to present such values as 176 and 234 millimeters of mercury, the corresponding maximum pressure in the aorta being 158 and 212 millimeters respectively.[2] The maximum pressures obtained from simultaneous observations upon the right and left ventricle of a dog are variously reported. It would perhaps be not far wrong to say that in this animal the pressure in the right ventricle is to that in the left as 1 to 2.6.[3]

The work done by each ventricle during its systole is found by multiplying the weight of the pulse-volume ejected into the force put forth in ejecting it. That force is equal to the pressure under which the pulse volume is expelled. If we use as a basis of calculation the pressures observed in the dog's heart with the maximum manometer, we may assume as the measure of a given pressure within the contracting human left ventricle 200 millimeters of mercury, and for the human right ventricle 77 millimeters. If for each column of mercury there be substituted the corresponding column of blood, the heights will be 2.567 meters and 0.988 meter respectively. The force exerted by the right or left ventricle upon the pulse-volume might therefore just equal that put forth in lifting it to a height of 0.988 or 2.567 meters. If we assume 100 grams as the weight of a possible pulse-volume ejected by a human ventricle, the work done at each systole of the left ventricle would be $100 \times 2.567 = 256.7$ grammeters, and at each systole of the right ventricle $100 \times 0.988 = 98.8$ grammeters ; a grammeter being the work done in raising one gram to the height of one meter. The work of both ventricles together would be $256.7 + 98.8 = 355.5$ grammeters. The foregoing estimates are offered not as statements of what does occur, but as very rough indications of what may occur. Even

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[1] F. Goltz und J. Gaule : "Ueber die Druckverhältnisse im Innern des Herzens," *Archiv für die gesammte Physiologie*, 1878, xvii. p. 100.

[2] S. de Jager : "Ueber die Saugkraft des Herzens," *Pflüger's Archiv für die gesammte Physiologie*, 1883, pp. 504, 505. [3] Goltz und Gaule, *op. cit.*, p. 106.

thus, however, they are of moment.   When we think of the vast number of beats executed by the heart every day, the great amount of energy rendered manifest in maintaining the circulation becomes apparent, and our interest is heightened in the fact that all of this large sum of energy is liberated in the muscular tissue of the heart itself.   Thus, too, the physiological significance of the diastole is accentuated as a time of rest for the cardiac muscle, as well as a necessary pause for the admission of blood into the ventricle.   To disregard minor considerations, the work done at a systole will evidently depend upon the amount of the pulse-volume, of the arterial pressure overcome, and of the velocity imparted to the ejected blood.   All these are variable.   The work of the ventricles therefore is eminently variable.

The Heart's Contraction as a Source of Heat.—In dealing with the movement of the blood in the vessels we have seen that the energy of visible motion liberated by the cardiac contractions is progressively changed into heat by the friction encountered by the blood ; and that this change is nearly complete by the time the blood has returned to the heart, the kinetic energy of each systole sufficing to drive the blood from the heart back to the heart again, but probably not being much more than is required for this purpose.   Practically, therefore, all the energy of the heart's contraction becomes heat within the body itself, and leaves the body under this form.   As the heart liberates during every day an amount of energy which is always large but very variable, its contractions evidently make no mean contribution to the heat produced in the body and parted with at its surface.

H. The Mechanism of the Valves of the Heart.

Use and Importance of the Valves.—The discussion just concluded shows the work of the heart to be the forcible pumping of a variable pulse-volume out of veins where the pressure is low into arteries where the pressure is high.   It is owing to the valves that this is possible, and so dependent is the normal movement of the blood upon the valves at the four ventricular apertures that the crippling of a single valve by disease may suffice to destroy life after a longer or shorter period of impaired circulation.

The Auriculo-ventricular Valves.—The working of the auriculo-ventricular valves (see Fig. 103) is not hard to grasp.   When the pressure within the ventricle in its diastole is low, the curtains hang free in the ventricle, although probably never in close contact with its wall.   As the blood pours into the ventricle, the pressure within it rises, currents flow into the space between the wall and the valve, and probably bring near together the edges of the curtains and also their surfaces for some distance from the edges.   Thus, upon the cessation of the auricular systole, the supervening of a superior pressure within the ventricle probably applies the already approximated edges and surfaces of the curtains to one another so promptly that the commencing contraction of the ventricle is not attended by regurgitation into the auricle. The principle of closure is the same for the tricuspid valve as for the mitral.   As the forces are exactly equal and opposite which press together the

opposed parts of the surfaces of the curtains, those parts undergo no strain, and hence are enabled to be exquisitely delicate and flexible and therefore easily fitted to one another. On the other hand, the parts of the valve which intervene between the surfaces of contact and the auriculo-ventricular ring are tough and much thicker, as they have to bear the brunt of the pressure within the contracting ventricle. As the systole of the ventricle increases, the auriculo-ventricular ring probably becomes smaller, and the curtains of the valve probably become somewhat fluted from base to apex, so that their line of contact is a zig-zag. At the same time their surfaces of contact may increase in extent.

Tendinous Cords and their Uses.—The structure so far described is wonderfully effective because it is combined with an arrangement to prevent a reversal of the valve into the auricle, which otherwise would occur at once. This arrangement consists in the disposition of the tendinous cords, which act
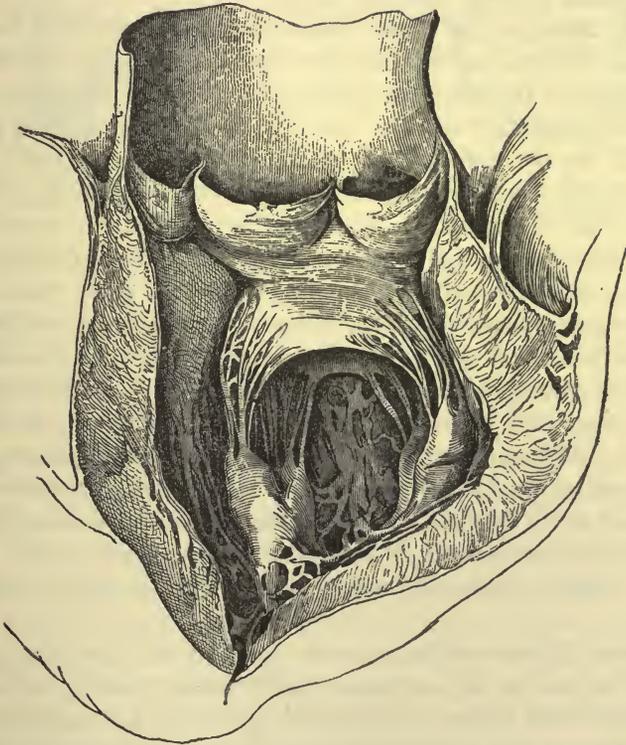
Fig. 103.—The left ventricle and aorta laid open, to show the mitral and aortic semilunar valves (Henle).

as guy-ropes stretched between the muscular wall of the ventricle and the valve, whether mitral or tricuspid. These cords are tough and inelastic, and, like the valve, are coated with the slippery lining of the heart. They are stout where they spring from the muscle, but divide and subdivide into branches, strong but sometimes very fine, which proceed fan-wise from their

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stem to their insertions (see Fig. 103). These insertions are both into the free margin of the valve and into the whole extent of that surface of it which looks toward the wall of the ventricle, quite up to the ring. By means of this arrangement of the cords each curtain is held taut from base to apex throughout the systole of the ventricles, the opposed surfaces being kept in apposition, and the parts of the curtains between these surfaces and the ring being kept from bellying unduly toward the auricle. Each curtain is held sufficiently taut from side to side as well, because the tendinous cords inserted into one lateral half of the curtain spring from a widely different part of the wall of the heart from those of the other lateral half of it (see Fig. 103). At all times, therefore, even when the walls of the ventricle are most closely approximated during systole, the cords may pull in slightly divergent directions upon the two lateral halves of each curtain. This arrangement of the cords may also cause them, when taut, to pull in slightly convergent directions upon the contiguous lateral halves of two neighboring curtains and thus to favor the pressing of them together (see Fig. 103).

Papillary Muscles and their Uses.—In the left ventricle the tendinous cords arise in two groups, like bouquets, from two teat-like muscular projections which spring from opposite points of the wall of the heart, and which are called the "papillary muscles" (see Fig. 103). One of these gives origin to the cords for the right half of the anterior and for the right half of the posterior curtain; the other papillary muscle gives rise to the cords for the left halves of the two curtains. Each papillary muscle is commonly more or less subdivided (see Fig. 103). The same principles are carried out, but less regularly, for the origins of the tendinous cords of the more complex tricuspid valve. Various opinions have been held as to the use of the papillary muscles. It seems probable that during the change of size and form wrought in the ventricle by its systole, the origins of the tendinous cords and the auriculo-ventricular ring tend to be approximated and the cords to be slackened in consequence. Perhaps this is checked by a compensatory shortening of the papillary muscles, due to their sharing in the systolic contraction of the muscular mass of which they form a part. Observations have recently been made which have been interpreted to mean that the papillary muscles begin their contraction slightly later and end it slightly earlier than the mass of the ventricle.[1]

Semilunar Valves.—The anatomy and the working of the semilunar valves are the same in the aorta as in the pulmonary artery, and one account will answer for both valves. Each valve is composed of three entirely separate segments, set end to end within and around the artery just at its origin from the ventricle. The attachments of the segments occupy the entire circumference of the vessel (Fig. 103). Like the tricuspid and mitral valves, each semilunar segment is composed of a sheet of tissue which is tough, thin, supple, and slippery; but the semilunar valves differ from the tricuspid and

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[1] C. S. Roy and J. G. Adami: "Heart-beat and Pulse-wave," *The Practitioner*, 1890, i. p. 88.

mitral, not only in the complete distinctness of their segments, but also in their mechanism. The tendinous cords are wholly lacking, and each segment depends upon its direct connection with the arterial wall to prevent reversal into the ventricle during the diastole of the latter. If the artery be carefully laid open by cutting exactly between two of the segments, each of the three is seen to have the form of a pocket with its opening turned away from the heart (see Fig. 103). Behind each segment, the artery is dilated into one of the hollows or "sinuses" of Valsalva.[1] As the valve lies immediately above the base of the ventricle the segments rest upon the top of the thick muscular wall of the latter, which affords them a powerful support (see Fig. 104). Each segment is attached by the whole length of its longer edge to the artery, while the free margin is·formed by the shorter edge. It is this arrangement which renders reversal of a segment impossible (see Fig. 103).
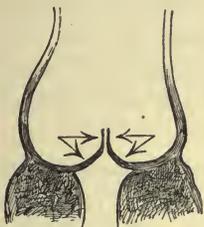
FIG. 104.—Diagram to illustrate the mechanism of the semilunar valve.
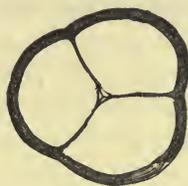
FIG. 105.—Diagram to illustrate the mechanism of the semilunar valve and corpora Arantii.

While the blood is streaming from the ventricle into the artery, the three segments are pressed away by the stream from the centre of the vessel, but never nearly so far as to touch its wall. At all times, therefore, a pouch exists behind each segment, which pouch freely communicates with the general cavity of the artery. As the ventricular systole nears its end, the ventricular cavity doubtless becomes narrowed just below the root of the artery, and with it the arterial aperture itself, while currents enter the sinuses of Valsalva. Thus for a double reason the three segments of the valve are approximated, and probably the last blood pressed out of the ventricle issues through a narrow chink between them. The instant that the pressure in the ventricle falls below the arterial pressure, the three segments must be brought together by the superior pressure within the artery, and tightly closed by its forcible recoil, without regurgitation having occurred in the process (see Figs. 104, 105).[2]

Lunulæ and their Uses.—Each segment of a semilunar valve, when closed, is in firm contact with its fellows not only at its free margin but also over a considerable surface, marked in the anatomy of the segment by the two "lunulæ" or little crescents, each of which occupies the surface of the segment from one of its ends to the middle of its free margin, the shorter edge

[1] Named from the Italian physician and anatomist Valsalva of Bologna, bòrn in 1666.

[2] L. Krehl: "Beiträge zur Kenntniss der Füllung und Entleerung des Herzens," *Abhandlungen der math.-physischen Classe der k. sächsischen Gesellschaft der Wissenschaften*, 1891, Bd. xvii. No. 5, p. 360.

of the lunula being one-half of the free margin of the segment (see Fig. 103). Over the surface of each lunula each segment is in contact with a different one of its two fellows (see Fig. 105). The firmness of closure thus secured is shown by Figure 104, which represents a longitudinal section of the artery, passing through two of the closed segments. The forces which press together the opposed surfaces are equal and opposite, and the parts of the segments which correspond to these surfaces undergo no strain. The lunulæ, therefore, like the mutually opposed portions of the mitral or tricuspid valve, are very delicate and flexible, while the rest of each semilunar segment is strongly made, to resist of itself the arterial pressure.

Corpora Arantii and their Uses.—At the centre of the free margin of each semilunar segment, just between the ends of the two lunulæ, there is a small thickening, more pronounced in the aorta than in the pulmonary artery, called the "body of Aranzi"[1] (corpus Arantii). This thickening both rises above the edge and projects from the surface between the lunulæ. When the valve is closed, the three corpora Arantii come together and exactly fill a small triangular chink, which otherwise might be left open just in the centre of the cross section of the artery (see Figs. 103, 105).

The foregoing shows that the mechanism of the semilunar valves is no less effective, though far simpler, than that of the mitral and tricuspid. That the latter two should be more complex is natural; for each of them must give free entrance to and prevent regurgitation from a chamber which nearly empties itself, and hence undergoes a very great relative change of volume; while the arterial system is at all times distended and undergoes a change of capacity which is relatively small while receiving a pulse-volume and transmitting it to the capillaries.

I. THE CHANGES IN FORM AND POSITION OF THE BEATING HEART, AND THE CARDIAC IMPULSE.

General Changes in the Heart and Arteries.—During the brief systole of the auricles these diminish in size while the swelling of the ventricles is completed. During the more protracted systole of the ventricles, which immediately follows, these diminish in size while the auricles are swelling and the injected arteries expand and lengthen. During the greater part of the succeeding diastole of the ventricles both these and the auricles are swelling, and all the muscular fibres of the heart are flaccid, up to the moment when a new auricular systole completes the diastolic distention of the ventricles, as above stated. During the ventricular diastole, as the great arteries recoil they shrink and shorten. The changes of size in the beating heart depend entirely upon the changes in the volume of blood contained in it, and not upon changes in the volume of the muscular walls. The muscular fibres of the heart agree with those found elsewhere in not changing their volume appreciably during contraction, but their form only. The cardiac cycle thus runs its course with

[1] Named from Julius Cæsar Aranzi of Bologna, an Italian physician and anatomist, born in 1530.

regularly recurring changes of size in the auricles, the ventricles, and the arteries. These changes of size are accompanied by corresponding changes in the form and position of the heart, which are both interesting in themselves and important in relation to the diagnosis of disease. The basis of their study consists in opening the chest and pericardium of an animal, and seeing, touching, and otherwise investigating the beating heart. The changes in the beating heart, moreover, underlie the production of the so-called cardiac impulse, or apex-beat, which is of interest in physical diagnosis.

Observation of the Heart and Vessels in the Open Chest.—The beating heart may be exposed for observation in a mammal by laying it upon its back, performing tracheotomy, and completely dividing the sternum in the median line, beginning at the ensiform cartilage. Artificial respiration is next established, a tube having been tied into the trachea before the chest was opened. The two sides of the chest are now drawn asunder and the pericardium is laid open to expose the heart.

If, in any mammal, the ventricles be lightly taken between the thumb and forefinger, the moment of their systole is revealed by the sudden hardening of the heart produced by it, as the muscular fibres contract and press with force upon the liquid within. On the other hand, the ventricular diastole is marked by such flaccidity of the muscular fibres that very light pressure indents the surface, and causes the finger to sink into it, in spite of care being taken to prevent this. Commonly, therefore, at the systole the thumb and finger are palpably and visibly forced apart, no matter where applied, in spite of the fact that the volume of the ventricles is diminishing. This sinking of the finger or of an instrument into the relaxed wall of the heart has given rise to many errors of observation regarding changes during the beat. The time when the ventricles are hardened beneath the finger coincides with the up-stroke of the arterial pulse near the heart, and, as shown by Harvey,[1] with the time when an intermittent jet of blood springs from a wound of either ventricle. The hardening is proven thus to mark the systole of the ventricles. Those changes of size, form, and position of the exposed heart which accompany the hardening of the ventricles beneath the finger are therefore the changes of the ventricular systole; and the converse changes are those of the ventricular diastole. To interpret all the changes correctly by the eye alone, without the aid of the finger or of the jet of blood, is a task of surpassing difficulty in a rapidly beating heart, as was eloquently set forth by Harvey.[2]

Changes of Size and Form in the Beating Ventricles.—In a mammal, lying upon its back, with the heart exposed, the ventricles evidently become smaller during their systole. Their girth is everywhere diminished and their length also, the latter much less than the former; indeed the diminution in length is a disputed point. Not merely a change of size, but a

[1] *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, 1628, p. 23; Willis' translation, Bowie's edition, 1889, p. 23.

[2] *Op. cit.*, 1628, p. 20; Willis' translation, Bowie's edition, p. 20.

change of form is thus produced; the heart becomes a smaller and shorter, but a more pointed, cone. The systolic narrowing from side to side is very conspicuous. In a mammal lying on its back, this narrowing is accompanied by some increase in the diameter of the heart from breast to back so that the surface of the ventricles toward the observer becomes more convex. Thus the base of the ventricles, which tended to be roughly elliptical during their relaxation, tends to become circular during their contraction; and the diameter of the circle is greater than the shortest diameter of the ellipse, which latter diameter extends from breast to back. At the same time, the area of the base when circular and contracted is much less than when elliptical and relaxed.[1] Naturally, none of these comparisons to mathematical figures makes any pretence to exactness. At the same time that the contracting heart undergoes these changes, the direction of its long axis becomes altered. In animals in which the heart is oblique within the chest, the line from the centre of the base to the apex, that is, the long axis, while it points in general from head to tail, points also toward the breast and to the left. In an animal lying on its back, the ventricles when relaxed in diastole tend to form an oblique cone, the apex having subsided obliquely to the left and toward the tail. As the ventricles harden in their systole, they tend to change from an oblique cone to a right cone; the long axis tends to lie more nearly at right angles to the base; and consequently the apex, unfettered by pericardium or chest-wall, makes a slight sweep obliquely toward the head and to the right, and thus rises up bodily for a little way toward the observer. This movement was graphically called by Harvey the erection of the heart.[2] It is accompanied by a slight twisting of the ventricles about their long axis, in such fashion that the left ventricle turns a little toward the breast, the right ventricle toward the back. This twisting movement is probably due simply to the course of the cardiac muscular fibres.

Changes of Position in the Beating Ventricles.—The changes in form imply changes in position. The oblique movement of the long axis implies that in systole the mass of the ventricles sweeps over a little toward the median line and also a little toward the head. The shortening of the long axis implies that either the apex recedes from the breast, or the base of the ventricles recedes from the back, or both. Of these last three possible cases, the second is the one that occurs. The oblique movement of the apex is accompanied by no recession of it; but the auriculo-ventricular furrow and the roots of the aorta and pulmonary artery move away from the spinal column as the injected arteries lengthen and expand, and, as the auricles swell, during the contraction of the ventricles. During their diastole the ventricles are soft; they swell; and changes of form and position occur which need not be detailed now, as they are simply converse to those of the systole and have been indicated already in dealing with the latter.

[1] C. Ludwig: "Ueber den Bau und die Bewegungen der Herzventrikel," *Zeitschrift für rationelle Medizin*, 1849, vii. p. 189.

[2] *Op. cit.*, 1628, p. 22. Translation, 1889, p. 22.

Changes in the Beating Auricles.—Except in small animals, the walls of both the ventricles are so thick that the color of the two is the same and is unchanging, namely, that of their muscular mass; but the walls of the auricles are so thin that their color is affected by that of the blood within, so that the right auricle looks bluish and dark and the left auricle red and bright. During the brief systole of the auricles they are seen to become smaller and paler as blood is expelled from them, while their serrated edges and auricular appendages shrink rapidly away from the observer. The changes of the auricular systole are seen to precede immediately the changes of the systole of the ventricles and to succeed the repose of the whole heart. During the relatively long diastole of the auricles these are seen to swell, whether the ventricles are shrinking in systole or are swelling during the first and greater part of their diastole.

Changes in the Great Veins.—In the venæ cavæ and pulmonary veins a pulse is visible, more plainly in the former than in the latter, which pulse has the same rhythm as that of the heart's beat. The causes of this pulse are complex and imperfectly understood. It depends in part upon the rhythmic contraction of muscular fibres in the walls of the veins near the auricles, which must heighten the flow into the latter, and which contraction the auricular systole immediately follows.[1] This venous pulse will be mentioned again in discussing the details of the events of the cycle (see p. 430).

Changes in the Great Arteries.—It is interesting to note that even in so large an animal as the calf the pulse of the aorta or of the pulmonary artery can hardly be appreciated by the eye, so far as the increase in girth of either vessel is concerned. The expansion of the artery affects equally all points in its circumference, and being thus distributed, is so slight in proportion to the girth of the vessel that the profile of the latter scarcely seems to change its place. The lengthening of the expanding artery can be more readily seen.

Effects of Opening the Chest.—Such are the changes observed in the heart and vessels when exposed in the opened chest of a mammal lying on its back. The question at once arises, Can these changes be accepted as identical with those which occur in the unopened chest of a quadruped standing upon its feet, or of a man standing erect? It will be most profitable to deal at once with the case of the human subject. What are the possible, indeed probable, differences between the changes in the heart in the unopened upright chest and in the same when opened and supine?

When air is freely admitted to both pleural sacs, all those complex effects upon the circulation are at once abolished which we have seen to be caused by the elasticity of the lungs and the movements of respiration. The artificial respiration will have an effect upon the pulmonary transit of the blood and so upon the circulation; but the details of this effect are not the same as those of natural respiration, and, for our present purpose, may be disregarded.

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[1] T. Lauder Brunton and F. Fayrer: "Note on Independent Pulsation of the Pulmonary Veins and Vena Cava," *Proceedings of the Royal Society,* 1876, vol. xxv. p. 174.

What has been abolished is the continual suction, rhythmically increased in inspiration, exerted by the lungs upon the heart and all the vessels within the chest, which suction at all times favors the expansion and resists the contraction of the cavities of the heart and of the vessels. On the opening of both pleural sacs the heart and vessels are exposed to the undiminished and unvarying pressure of the atmosphere. Moreover, the heart has ceased to be packed, as it were, between the pleuræ and lungs to right and left, the spine, the front of the chest-wall, and the diaphragm. From these considerations it follows that the heart must be freer to change its form and position in the opened than in the unopened chest; and that these changes must be more modified by simple gravity in the former case than in the latter. Even in the open chest we have studied these changes only in an animal lying on its back. But if we turn the creature to either side, or place it upright in imitation of the natural human posture, the ventricles of the exposed heart in any case tend to assume, in systole, the same form, which has been compared roughly to a right cone with a circular base. This is the form proper to the hardened structure of branching and connected fibres of which the contracting ventricles consist. But if the exposed ventricles be noted in diastole, it will appear that their form depends very largely upon the effects of gravity upon the exceedingly soft and yielding mass formed by their relaxed fibres. We have seen them, in diastole, to flatten from breast to back, to spread out from side to side, to gravitate toward the tail and to the left. If the animal is laid on its side, they flatten from side to side, they spread out from breast to back, and gravitate to the right or left, as the case may be.[1]

Probable Changes in the Heart's Form and Position in the Unopened Chest.—It is fair to conjecture that the increase of the relaxed ventricles in girth and in length which is seen in the open chest would not be greatly different in the closed chest of a man in the upright posture. But it is probable that the flattening of the exposed heart from breast to back, which is seen in diastole, would not occur if the chest were closed. It is precisely in this direction that the flaccid heart exposed in the supine chest would be flattened unduly by its own weight, when deprived of many of its anatomical supports and of the dilating influence of the lungs. The flattening from breast to back must cause an exaggerated spreading out from side to side and hence an unduly elliptical form of the base, inasmuch as, at the same time, the girth of the ventricles is increasing as they enlarge in their diastole. Conversely, it is probable, both *a priori* and from experimental evidence, that in the chest, when closed and upright, the diminution in size of the contracting ventricles proceeds more symmetrically; that their girth everywhere diminishes through a diminution of the diameter from breast to back as well as of that from side to

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[1] J. B. Haycraft: "The Movements of the Heart within the Chest-cavity, and the Cardiogram," *The Journal of Physiology*, vol. xii., Nos. 5 and 6, December, 1891, p. 448; J. B. Haycraft and D. R. Paterson: "The Changes in Shape and in Position of the Heart during the Cardiac Cycle," *The Journal of Physiology*, vol. xix., Nos. 5 and 6, May, 1896, p. 496.

side, and not through an exaggerated lessening of the latter and an actual increase of the former. In this case, too, the base would tend to become more circular during the systole by means of a less marked change from the diastolic form.[1]

It has been said that in systole the ventricles are somewhat shortened in the exposed heart, and probably also in the unopened human chest. In the open chest the apex does not recede at all in virtue of this shortening; on the contrary, the base of the ventricles is seen to move toward the apex, and away, therefore, from the spine. Experiment has proven that the foregoing is true also of the unopened chest.[2] It has been noted already that this movement of the base, which in the upright chest would be a descent, is accompanied by a lengthening of the aorta and pulmonary artery as their distention takes place. Very probably it is the thrust of the lengthened arteries which largely causes the descent of the base of the contracting ventricles, which descent compensates for the shortening of the ventricles and retains the apex in contact with the chest-wall.

The Impulse or Apex-beat.—It must always have been a matter of common knowledge that, in man, a portion of the heart lies so close to the chest-wall that, at each beat, the soft parts of that wall may be seen and felt to pulsate over a limited area. This is commonly in the fourth or fifth intercostal space, midway between the left margin of the sternum and a vertical line let fall from the left nipple. A similar pulsation may be observed in other mammals. The protrusion of the chest-wall at the site of this "impulse" or "apex-beat" occurs when the arteries expand, and the up-stroke of their pulse is felt; and the recession of the chest coincides with the shrinking of the arteries away from the finger. The impulse proper, that is the protrusion of the chest-wall, occurs, therefore, at the time of the systole of the ventricles. By far the most important factor of the apex-beat is probably the effort of the hardening ventricles to change the direction of their long axis against the resistance of the chest-wall. A heart severed from the body and bloodless, if laid upon a table, lifts its apex as it hardens in systole and assumes its proper form. If a finger be placed near enough to the rising apex to be struck by it, the same sensation is received as from the impulse.

It is interesting to note that around the point where the soft parts of the chest are protruded by the impulse, they are found to be very slightly drawn in at the time of its occurrence. This drawing-in is called the "negative impulse," and must be caused by the diminution in size of the contracting ventricles. These are air-tight within the chest, and so their forcibly lessened surface must be followed down, in varying degrees, under the pressure of the atmosphere, by the elastic and yielding lungs and by the far less yielding soft parts of the chest-wall.

The apex-beat can be brought to bear in various ways upon a recording lever, and thus be made to inscribe upon the kymograph a rhythmically fluctuating trace, which is called a cardiogram. Considerable attention has been

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[1] J. B. Haycraft: *loc. cit.*   [2] Haycraft: *loc. cit.*

given to the elucidation of the curve thus recorded; but, so far, too little agreement has been reached for the subject to be entered upon here.[1]

J. The Sounds of the Heart.

If the ear be applied to the human chest, at or near the place of the apex-beat, the heart's pulsation will be heard as well as felt. This fact was known to Harvey.[2] About two hundred years later than Harvey, in 1819, the French physician Laënnec, the inventor of auscultation, made known the fact that each beat of the heart is accompanied not by one but by two separate sounds. He also called attention to their great importance in the diagnosis of the diseases of the heart.[3]

Relations of the Sounds.—The first sound is heard during the time when the apex-beat is felt; it therefore coincides with the systole of the ventricles. The second sound is much shorter, and follows the first immediately, or, to speak more strictly, after a scarcely appreciable interval. The second sound, therefore, coincides with the earlier part of the diastole of the ventricles. The second sound is followed in its turn by a period of silence, commonly longer considerably than the second sound, which silence lasts till the beginning of the first sound of the next ventricular beat. The period of silence, therefore, coincides with the later, and usually longer, portion of the diastole of the ventricles, and with the systole of the auricles. It is interesting that the great auscultator, Laënnec, offered no explanation of the cause of either sound, while he made and reiterated the incorrect and misleading statement that the second sound coincides with the systole of the auricles. When the heart beats oftener than usual, each beat must be accomplished in a shorter time; and it is found that, during a briefer beat, the period of silence is shortened much more than the period during which the two sounds are audible; which latter period may not be altered appreciably.

Characters of the Sounds.—The first sound is not only comparatively long, but is low-pitched and muffled. The second sound is comparatively short, and is high and clear. The two sounds, therefore, are sharply contrasted in duration, pitch, and quality. A rough notion of the contrasted characters of the sounds may be obtained by pronouncing the meaningless syllables "lubb dup." In other mammals the sounds have substantially the same characters as in man.

Cause of the Second Sound.—Since Laënnec's time, the cause of the second sound has been demonstrated by experiment. The second sound is due to the vibrations caused by the simultaneous closure of the semilunar valves of the pulmonary artery and of the aorta, when the diastole of the ventricles has just begun. This cause was first suggested by the French physician

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[1] M. von Frey: *Die Untersuchung des Pulses*, etc., 1892, p. 102; R. Tigerstedt: *Lehrbuch der Physiologie des Kreislaufes*, Leipzig, 1893, p. 112.

[2] *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, 1628, p. 30; Willis's translation, Bowie's edition, 1889, p. 34.

[3] R. T. H. Laënnec: *De l'auscultation médiate*, etc., Paris, 1819.

Rouanet in 1832;[1] not long afterward it was conclusively proven by experiment by the English physician C. J. B. Williams.[2]

Dr. Williams's experiment was as follows: In a young ass the chest was opened and the heart was exposed. It was ascertained that the second sound was audible through a stethoscope applied to the heart itself. A sharp hook was then passed through the wall of the pulmonary artery, and was so directed as to make the semilunar valve incompetent temporarily. By means of a second hook, the aortic semilunar valve was likewise made incompetent. When both hooks were in position, the heart was auscultated afresh, and the second sound was found to have disappeared, and to be replaced by a hissing murmur. The hooks were withdrawn during auscultation, and at the moment of withdrawal the murmur disappeared and the normal second sound recurred. Subsequent clinical and post-mortem observations have shown that the second sound may be altered by disease which cripples the aortic valves.

Causes of the First Sound.—The causes of the first sound have not been proven so clearly by the available evidence, which is partly experimental and partly derived from physical diagnosis followed by post-mortem verification. The first sound, like the second, was ascribed by Rouanet[3] to vibrations depending upon valvular closure,—the simultaneous closure of the tricuspid and mitral valves; but the persistence of the sound throughout the whole ventricular systole made this cause less probable than in the case of the second sound. Williams,[4] on the other hand, ascribed the first sound to the contraction of the muscular tissue of the ventricles,—an explanation consistent with the muffled quality of the first sound, and with its persistence throughout the systole of the ventricles. It is now believed by many that both of the foregoing explanations are correct, and that the first sound is composite in its origin, and due both to closure of the valves and to muscular contraction. The evidence in favor of these causes is, briefly, as follows:

In favor of a valvular element in the first sound, it may be urged: That if the ventricles of a dead heart be suddenly distended with liquid, the mitral and tricuspid valves produce a sound in closing; and that clinical and post-mortem observations show that the first sound may be altered by disease which cripples the auriculo-ventricular valves.

In favor of an element in the first sound caused by muscular contraction it may be urged: That in a still living but excised heart, the first sound continues to be heard under circumstances which preclude the closure and vibration of the valves, and leave in operation no conceivable cause for the first sound except muscular contraction. Experiments upon the first sound of the excised heart were reported in 1868 by Ludwig and Dogiel,[5] and were

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[1] J. Rouanet: *Analyse des bruits du cœur*, Paris, 1832.

[2] C. J. B. Williams: *Die Pathologie und Diagnose der Krankheiten der Brust, etc.* Nach der dritten, sehr vermehrten Auflage aus dem Englischen übersetzt, Bonn, 1838. (The writer has not seen an English edition.)   [3] *Loc. cit.*   [4] *Loc. cit.*

[5] J. Dogiel und C. Ludwig: "Ein neuer Versuch über den ersten Herzton," *Berichte über die Verhandlungen der k. sächsischen Gesellschaft der Wissenschaften zu Leipzig, math.-physische Classe*, 1868, p. 89.

performed upon the dog as follows: The heart was exposed during arti-
ficial respiration, and loose ligatures were placed upon the venæ cavæ, the
pulmonary artery, the pulmonary veins, and the aorta. Next, the loose
ligatures were tightened in the order above written, during which process
the beating heart necessarily pumped itself as free as possible of blood.
The vessels were then divided distally to the ligatures, and the heart was
excised and suspended in a conical glass vessel containing freshly drawn defi-
brinated blood, in which the heart was fully immersed without touching the
glass at any point. Under these conditions the excised heart might execute
as many as thirty beats. The conical glass vessel was supported in a "ring-
stand." The narrow bottom of the vessel consisted of a thin sheet of india-
rubber, with which last was connected the flexible tube and ear-piece of a
stethoscope. By means of the latter any sound produced by the beating
heart could be heard through the blood and the sheet of rubber. The second
sound was not heard; but at each contraction of the ventricles the first sound
was heard, not of the same length or loudness as normally, but otherwise unal-
tered. The conditions of experiment precluded error resulting from adventi-
tious sounds; moreover, the heart before excision had pumped itself free of
all but a fraction of the amount of blood required to close the valves, and
had been so treated that no more could enter. It was therefore practically
impossible that the sound heard could have its origin at the valves; and no
origin remained conceivable other than in the muscular contraction of the ven-
tricular systole. Later experiments, in which the auriculo-ventricular valves
have been rendered incompetent by mechanical means, have seemed to confirm
the importance of muscular contraction as a cause of the first sound.[1]

Acoustic Analysis of the First Sound.—By the use of a stethoscope
combined with a peculiar resonator, the German physician Wintrich of Erlan-
gen[2] satisfied himself that he could analyze the first sound upon auscultation,
so as to detect in it two components, one higher pitched, which he attributed
to the vibration of the auriculo-ventricular valves, and a component of lower
pitch, attributed to the muscular contraction of the heart. The other experi-
ments above referred to, however, which sustain muscular contraction as a cause
of the first sound, did not reveal a change of pitch following incompetence
of the valves, but only a diminution in loudness and duration.

K. The Frequency of the Cardiac Cycles.[3]

In a healthy full-grown man, resting quietly in the sitting posture, the
heart beats on the average about 72 times a minute. In the full-grown

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[1] L. Krehl: "Ueber den Herzmuskelton," *Archiv für Anatomie und Physiologie*, Physiolo-
gische Abtheilung, 1889, p. 253; A. Kasem-Bek: "Ueber die Entstehung des ersten Herztones,"
Pflüger's Archiv für die gesammte Physiologie, 1890, Bd. xlvii. p. 53.

[2] Wintrich: "Experimentalstudien über Resonanzbewegungen der Membranen," *Sitzungs-
berichte der phys.-med. Societät zu Erlangen*, 1873; Wintrich: "Ueber Causation und Analyse
der Herztöne," *Ibid.*, 1875.

[3] Tigerstedt: *Lehrbuch der Physiologie des Kreislaufes*, Leipzig, 1893, pp. 25–35; Vierordt:
Daten und Tabellen zum Gebrauche für Mediciner, 1888, pp. 105–109, 259.

woman the average is slightly higher, perhaps 80 to the minute. The heart beats less frequently in tall people than in short ones. The difference between men and women largely depends upon this, but careful observation shows that in the case of men and women of the same stature the heart-beats are slightly more frequent in the women. There is, therefore, a real difference as to the pulse between the sexes. Shortly before and after birth the heart-beats are very frequent, from 120 to 140 to the minute. During childhood and youth, the frequency diminishes gradually, the average falling below 100 to the minute at about the sixth year, and below 80 to the minute at about the eighteenth year. In extreme old age the pulse becomes slightly increased in frequency. It must, however, be borne in mind that there are very wide differences between individuals as to the average frequency of the heart-beats. Pulses of 40 and even fewer strokes to the minute, or, on the other hand, of more than 100 to the minute, are natural to some healthy people.

In every individual the frequency of the pulse varies decidedly, and may vary very greatly, during each twenty-four hours. It is least during sleep, and less in the lying than in the sitting posture. Standing makes the heart beat oftener, the difference being greater between standing and sitting than between sitting and lying. During muscular exercise the pulse-rate is much increased, violent exercise carrying it possibly to 150 or even more. Thermal influences have a marked effect, a hot bath, for instance, heightening the frequency of the pulse and a cold bath diminishing it. The taking of a meal also commonly puts up the frequency. The influence of emotion upon the heart's contractions is well known. It may act either to heighten the rate or to lower it. Finally, the practising physician soon learns that the heart's rate is more easily affected by comparatively slight causes, emotional or otherwise, in women, and especially in children, than in men—a fact of some importance in diagnosis.

The causes of the differences referred to in this section are partly unknown, and partly belong to the subject of the regulation of the circulation.

L. The Relations in Time of the Main Events of the Cardiac Cycle.

We have now considered the effects produced by the cardiac pump; its general mode of working; and the actual frequency of its strokes. We must next study certain important details relating to the individual strokes or beats of the ventricles and of the auricles. For this study the basis has already been laid in the sections headed " Causes of the Blood-flow " (p. 369), " Mode of Working of the Pumping Mechanism " (p. 370), " The Cardiac Cycle " (p. 396), and " Use and Importance of the Valves " (p. 400). These sections should now be read again in the order just given. Details can best be dealt with if we use, instead of the more familiar word " beat," the more technical one " cycle."

The Auricular Cycle; the Ventricular Cycle; the Cardiac Cycle.— Each systole and succeeding diastole of the auricles constitute a regularly

recurring pair of events which may truly be spoken of as an "auricular cycle;" and so also it is exact to say that the ventricles have their cycle, consisting of systole and succeeding diastole. As soon, however, as we strive for clearness, we find that the useful phrase "cardiac cycle" is necessarily arbitrary and imperfect. A perusal of the account given on p. 370 of the "Mode of Working of the Pumping Mechanism" shows at once that each auricular cycle, consisting of systole followed by diastole, must begin shortly before the corresponding ventricular cycle begins, and must end shortly before the corresponding ventricular cycle ends. The pumping mechanism is such that the auricular systole is completed just before the ventricular systole begins. The phrase "cardiac cycle" implies a reference to both auricular and ventricular events; if now we assume that the beginning of the auricular systole marks the beginning of the cardiac cycle, this must end either with the end of the auricular diastole or with the end of the ventricular diastole. In the former case the cardiac cycle would coincide with the auricular cycle, but would begin before the end of one ventricular diastole and would end before the end of another, thus containing no one complete ventricular diastole. In the second case, the cardiac cycle would contain one complete ventricular diastole and a fraction of another, and would also contain two auricular systoles. The second case is clearly even more objectionable than the first. The cardiac cycle had best be defined as consisting of all the events both auricular and ventricular which occur during one complete auricular cycle. The above discussion deals with a phrase which is a constant stumbling-block to students; and the question may well be asked, Why should the expression "cardiac cycle" not be abolished? The answer is, that this phrase is indispensable in order to accentuate certain important relations of the auricular cycle to the ventricular. During a heart-beat there is a period when the auricles and ventricles are in diastole at the same time. During this period, as we have seen, blood is passing from the veins directly through the auricles into the ventricles, and all the muscular fibres of the heart are resting. This period is therefore called that of "the repose of the whole heart," or the "pause." Whenever the heart is not wholly at rest, either auricles or ventricles must be in systole. We see, therefore, that each cardiac cycle must coincide with an auricular systole, the instantly succeeding ventricular systole, and a period of repose of the whole heart; and it is precisely these two systoles and the succeeding universal rest which most engage the attention when the beating heart is looked at in the opened chest. These three phenomena, it will be noted, exactly coincide with one complete auricular cycle, and so do not confuse the definition of the cardiac cycle which has been given already. We see, therefore, that the phrase which seemed at first so misleading has a real value, and will cease to confuse if its limitations be carefully noted.

The Brevity and Variability of Each Cycle.—From the frequency with which the cycles recur, it follows at once that each one, with its complex changes in the walls, chambers, and valves, is very rapidly performed. If, for

instance, the heart beat 72 times in one minute, each cycle occupies only a little more than 0.83 of a second. The brevity of each cycle is both an important physiological fact and a cause of difficulty in studying details. Each cycle, however, necessarily is capable of completion in much less time if the pulse-rate rise; for instance, during exercise. If repeated 144 times a minute instead of 72 times, each cycle would occupy only one-half of its previous time of completion. With a pulse of less than 60, again, each cycle would occupy over one second.

Relative Lengths of the Ventricular Systole and Diastole.—An important question is whether or no there is any fixed relation between the time required for a systole of the ventricles and the time required for a diastole. When the length of the cycle changes from one second to one-half a second, will the length of the systole be diminished by one-half, and that of the diastole also by one-half? Or is a nearly invariable time required for the ventricles to do their work of ejection, while the period of rest and of receiving blood can be greatly shortened, for a while at least? The answer is that, while both systole and diastole may vary in length, the length of the systole is much the less variable, while the diastole is greatly shortened or lengthened according as the heart beats often or seldom.

These facts have been ascertained as follows: A trained observer[1] auscultated the sounds of the human heart during a number of cycles, and, at the instant when he heard the beginning either of the first or of the second sound, made a mark upon the revolving drum of a kymograph by means of a signalling apparatus. Of course, careful account was taken of the time lost between the occurrence of a sound and the recording of it. It was found that the time between the beginning of the first and that of the second sound did not vary to the same degree as the frequency of the beats. Although the interval in question may not be an exact measure of the period of ventricular systole, it is sufficiently near it for the purposes of this observation.

A second method[2] depended upon the interpretation of the curve inscribed by a lever pressed upon the skin over a pulsating human artery. Such a curve exhibits two sudden changes of direction, which were taken to indicate approximately the beginning and end of the injection of blood by the ventricle, and, therefore, to afford a rough measure of the duration of its systole. While the interpretation of the curve in question is not wholly settled, it seems, nevertheless, to give a fair basis for conclusions as to the present question. The figures resulting from the second method are especially instructive. It was found that, with a pulse of 47 to the minute, the approximate length of the ventricular systole was 0.347 of a second; of the diastole, 0.930 of a second. With a pulse of 128 to the minute, while the systole was only moderately diminished,

[1] F. C. Donders: "De Rhythmus der Hartstoonen," *Nederlandsch Archief voor Genees- en Natuurkunde,* 1865, p. 141.

[2] E. Thurston: "The Length of the Systole of the Heart as Estimated from Sphygmographic Tracings," *Journal of Anatomy and Physiology,* 1876, vol. x. p. 494.

viz. to 0.256 of a second, the diastole was reduced to 0.213 of a second—an enormous decline.

These results upon the human subject have been confirmed upon animals by experiments in which were registered the movements of a lever laid across the exposed heart;[1] or the fluctuations of the pressures within the ventricles.[2]

By whatever means investigated, the ventricular systole is found to be shortened with the cycle, and to be lengthened with it; the diastole is shortened or lengthened much more, however. In fact, if the pulse become very frequent, the diastole may be so shortened that the "pause" nearly disappears, and the systole of the auricles follows speedily after the opening of the cuspid valves. This signifies that, for a time, the cardiac muscle can do with very little rest, and that effective means exist for a very rapid "charging" of the ventricular cavity when necessary. For the working period of the ventricle, however, a more uniform time is required. For the average human pulse-rate this time of work is decidedly shorter than the time of rest—viz. about 0.3 of a second for the former as against about 0.5 for the latter.

Lengths of Auricular Events and of the Pause.—The systole of the auricles is very brief, being commonly reckoned at about 0.1 of a second, as the result of various observations.[3] At the average pulse-rate, therefore, the auricular systole is only about one-third as long as the ventricular, and the length of the auricular diastole is to that of the ventricular as seven to five. Consequently, a cardiac cycle of 0.8 of a second would comprise an auricular systole of 0.1 of a second; a ventricular systole of 0.3 of a second; and a pause, or repose of the whole heart, of 0.4 of a second—one-half of the cycle.

Practical Application.—The observations above described upon the interval between the beginnings of the sounds have a practical bearing upon physical diagnosis; for they show how faulty are the statements often made which assign regular proportions to the lengths of the sounds and the silences of the heart. The length of the "second silence" must be very fluctuating, as it comprises the longer part of the fluctuating ventricular diastole. The length of the first sound and of the very brief first silence together must be very constant, as they nearly coincide with the ventricular systole.

M. The Pressures within the Ventricles.[4]

We must now approach the study of further details of the working of the ventricular pumps, which details depend for their elucidation upon the measuring and recording of the pressures within the ventricles.

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[1] N. Baxt: "Die Verkürzung der Systolenzeit durch den Nervus accelerans cordis," *Archiv für Anatomie und Physiologie*, Physiologische Abtheilung, 1878, p. 122.

[2] M. von Frey und L. Krehl: "Untersuchungen über den Puls," *Archiv für Anatomie und Physiologie*, Physiologische Abtheilung, 1890, p. 31. W. T. Porter: "Researches on the Filling of the Heart," *Journal of Physiology*, 1892, vol. xiii. p. 531.

[3] H. Vierordt: *Daten und Tabellen zum Gebrauche für Mediciner*, 1888, p. 105.

[4] The matters connected with the ventricular pressure-curve may best be studied in the following writings, in which citations of other papers may be found: K. Hürthle, in *Pflüger's*

**Absolute Range of Pressure within the Ventricles and its Signifi-
cance.**—In dealing with the work done by the contracting ventricles (p. 398)
we have seen that the mercurial manometer, as used for studying the pressure
within the arteries, is quite unable to follow the changes of the intra-ventric-
ular pressure ; but that, by the intercalation of a valve, this instrument can be
converted into a useful " maximum manometer " for the measuring and record-
ing of the highest pressure occurring within the ventricle during a given time
—that is, during a certain number of cycles. It must now be added that by a
simple change of valves this same instrument can at any moment be changed
into a " minimum manometer."[1] We can thus, by means of the modified mer-
curial manometer, learn with fair correctness the extreme range of pressure
within the ventricles. As instances of the extent of this range, two observa-
tions may be cited upon the left ventricle of the dog, the chest not having been
opened. In one animal the maximum was found to be 234 millimeters of mer-
cury, the maximum pressure in the aorta being 212 millimeters ; and the min-
imum in the left ventricle was —38 millimeters—that is to say, 38 millimeters
less than the pressure of the atmosphere, the minimum pressure in the aorta
being 120 millimeters. In a second dog the figures were 176 and —30 milli-
meters for the ventricle, the aortic range being from 158 to 112 millimeters.[2]
In the right ventricle of the dog such ranges as from 26 to —8 millimeters,
from 72 to —25, and various intermediate values, have been noted, both in
the unopened and the opened chest.[3] For reasons already stated (p. 395) no
trustworthy figures can be given for the pressures in the pulmonary artery ;
but they can never fail to be less than the highest pressures within the right
ventricle.

The range of pressure, therefore, within either ventricle is in sharp contrast

Archiv für die gesammte Physiologie, as follows : "Zur Technik der Untersuchung des Blut-
druckes," 1888, vol. 43, p. 399. "Technische Mittheilungen," 1890, vol. 47, p. 1. " Ueber
den Ursprungsort der sekundären Wellen der Pulscurve," vol. 47, p. 17. "Technische Mit-
theilungen," 1891, vol. 49, p. 29. " Ueber den Zusammenhang zwischen Herzthätigkeit und
Pulsform," vol. 49, p. 51. " Kritik des Lufttransmissionsverfahrens," 1892, vol. 53, p. 281.
"Vergleichende Prüfung der Tonographen von Frey's und Hürthle's," 1893, vol. 55, p. 319.
K. Hürthle : "Orientirungsversuche über die Wirkung des Oxyspartein auf das Herz," *Archiv
für experimentelle Pathologie und Pharmakologie*, 1892, vol. xxx. p. 141. W. T. Porter : "Researches
on the Filling of the Heart," *The Journal of Physiology*, 1892, vol. xiii. p. 513. " A New Method
for the Study of the Intracardiac Pressure Curve," *Journal of Experimental Medicine*, vol. i.,
No. 2, 1896. M. von Frey und L. Krehl : "Untersuchungen über den Puls," *Archiv für
Anatomie und Physiologie*, Physiologische Abtheilung, 1890, p. 31. M. von Frey : "Die Unter-
suchung des Pulses," Berlin, 1892. "Das Plateau des Kammerpulses," *Archiv für Anatomie
und Physiologie*, Physiologische Abtheilung, 1893, p. 1. " Die Ermittlung absoluter Werthe für
die Leistung von Pulsschreibern," *Archiv für Anatomie und Physiologie*, Physiologische Abtheil-
ung, 1893, p. 17. "Zur Theorie der Lufttonographen," *Archiv für Anatomie und Physiologie*,
Physiologische Abtheilung, 1893, p. 204. " Die Erwärmung der Luft in Tonographen," *Cen-
tralblatt für Physiologie* vom 30 Juni 1894, Heft 7.

[1] F. Goltz und J. Gaule : " Ueber die Druckverhältnisse im Innern des Herzens," *Pflüger's
Archiv für die gesammte Physiologie*, 1878, xvii. p. 100.

[2] S. de Jager : " Ueber die Saugkraft des Herzens," *Pflüger's Archiv für die gesammte Physi-
ologie*, 1883, Bd. xxxi. p. 491.

[3] S. de Jager : *Loc. cit.*, pp. 506, 507 ; Goltz und Gaule : *Loc. cit.*, p. 106.

to that within the artery which it supplies with blood ; for the arterial pressure, although it fluctuates, is at all times far above that of the atmosphere, and is able, as we have seen, to maintain the circulation while the semilunar valve is closed and the ventricular muscle is at rest.   On the other hand, the pressure within the ventricle, when at its highest, rises decidedly above the highest arterial pressure, and thus the ventricle can overcome this and other opposing forces, open the valve, and expel the blood.   These facts have been stated already.   In falling, however, the pressure within the ventricle not only sinks below that in the artery, and so permits the semilunar valve to close, but sweeps downward to a point, it may be, below the pressure of the atmosphere, and, in so doing, falls below the pressure in the auricle, and permits the opening of the auriculo-ventricular valve and the entrance of blood out of the auricle and the veins.   As such a great range of pressure occurs in either ventricle of a heart which is repeating its cycles with entire regularity, it is presumable that at every cycle the pressure not only rises above that in the arteries but may sink below that of the atmosphere.

Methods of Recording the Course of the Ventricular Pressure.—It now becomes of interest to ascertain, if possible, not only the range, but the exact course, of these swift variations of pressure ; the causes of them, and the effects which accompany them.   It is hard to obtain, by the graphic method, a correct curve of the pressure within either ventricle.   We have seen that the mercurial manometer is useless for this purpose; and it is very difficult to devise any self-registering manometer which shall truly keep pace with fluctuations at once so great and so rapid.   The true form of this pressure-curve,
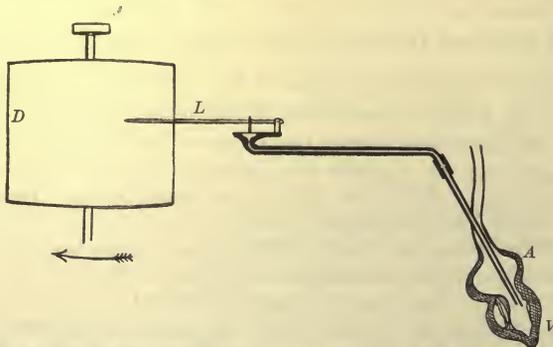
FIG. 106.—Diagram of the elastic manometer: *A*, auricle ; *V*, ventricle ; *D*, drum of the kymograph, revolving in the direction of the arrow, and covered with smoked paper; *L*, recording lever in contact with the revolving drum.   (The working details of the instrument are suppressed for the sake of clearness.)

therefore, still is partially in doubt, and is the subject of controversies which largely resolve themselves into contests between rival instruments.   We may pass by without mention methods which are either antiquated or little used. The following characters are common to the manometers with which the most serious attempts have lately been made to obtain a true and minute record of the fluctuations of pressure, even if great and rapid, within the heart or the vessels (see Fig. 106).   As in the case of the mercurial manometer, a cannula,

open at the end and charged with a fluid which checks the coagulation of the blood, is tied into a vessel, or, if the heart is under observation, is passed down into it through an opening in a jugular vein or a carotid artery. If the chest have been opened, the cannula may also be passed into the heart through a small wound in an auricle or even through the walls of the ventricle itself. The end of the cannula which remains without the animal's body is connected, air-tight, with a rigid tube of small, carefully chosen calibre, and as short as the conditions of the experiment permit. The other end of this tube is not, as in the mercurial manometer, left as an open mouth, but is connected, air-tight, with a very small metallic chamber, which constitutes, practically, a dilated blind extremity of the system formed by the tube and the cannula together. The roof of this small metallic chamber is a highly elastic disk either of thin metal or of india-rubber. Except for this small disk, all parts of the chamber, tube, and cannula are rigid. In the instruments of some observers, the entire cavity of the system formed by the chamber, tube, and cannula is filled with liquid, viz. the solution which checks coagulation. Other observers introduce this liquid only into the portion of the system nearest the blood ; the terminal chamber, and most of the rest of the system, containing only air. In every case the blood in the vessel or in the heart is in free communication, through the mouth of the tied-in cannula, with the cavity common to the tubes and to the terminal chamber. At every rise of blood-pressure a little blood enters this cavity, room being made for it by a displacement of liquid or of air, which in turn causes a slight bulging of the elastic disk. At every fall of blood-pressure a little blood mixed with liquid leaves the tubes as the elastic disk recoils. If the disk is of the right elasticity, its rise and fall are directly proportional to the rise and fall of the blood-pressure, and can be used to measure it. Upon the centre of the disk rests a delicate lever of the "third order," which rises and falls with the disk. The point of this lever traces upon the revolving drum of the kymograph a curve which records the fluctuations of the disk and therefore those of the blood-pressure. The elastic disk and the contents, together, of such an apparatus possess less inertia than mercury, and therefore follow far more closely rapid fluctuations of pressure. Such instruments may be called "elastic manometers," and are often called "tonographs," *i. e.* "tension-writers." They are of several forms.

It has been indicated already that the pressure of the blood may be communicated to the disk of an elastic manometer either by means of liquid or of air. A given series of fluctuations of blood-pressure may yield decidedly different curves according to the method of "transmission" employed to obtain them ; and the controversies as to the true form of the endocardiac pressure-trace turn upon the question whether such "transmission by air" or "transmission by liquid" yield the truer curve. The objections to the former method depend upon the readier compressibility of air ; the objections to transmission by liquid depend upon its greater inertia.

The General Characters of the Ventricular Pressure-curve.—Whatever kind of elastic manometer and of transmission be used, the curve

obtained shows certain characters which are recognized by all as properly-belonging to the changes of pressure within the ventricle, whether right or left. These general characters, moreover, persist after the opening of the chest. They are as follows (see Figs. 107, 108, 109): The muscular con-
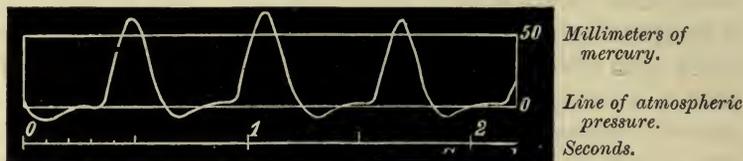
FIG. 107.—Magnified curve of the course of pressure within the right ventricle of the dog, the chest being open; to be read from left to right. Recorded by the elastic manometer, with transmission by air (von Frey).

traction of the systole begins quite suddenly, and produces a swift and extensive rise of pressure, marked in the curve by a line but slightly inclined from the vertical. In the same way the fall of pressure is nearly as sudden and as swift as the rise, and perhaps even more extensive. The systolic rise begins at a pressure a little above that of the atmosphere; the diastolic fall continues, toward its end, perhaps, with diminishing rapidity, till a point is reached often below the pressure of the atmosphere. The pressure then rises, perhaps continuing negative for a longer or shorter time, but presently becoming equal to that of the atmosphere. Near this it continues, perhaps with a gentle upward tendency, until, near the end of the ventricular diastole, the rise becomes more rapid to the point at which the succeeding ventricular systole is to begin.

It is the course of the pressure between its rapid rise and its rapid fall which has been the most disputed. The observers who employ manometers with liquid
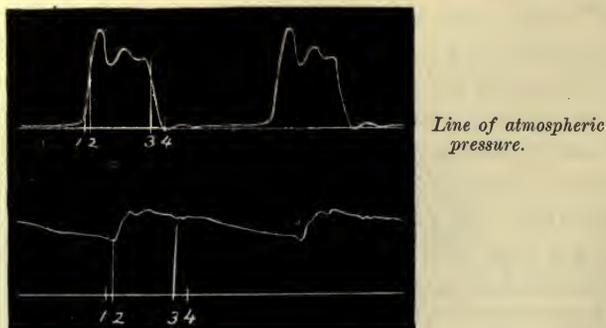
FIG. 108.—Magnified curve of the course of pressure within the left ventricle and the aorta of the dog, the chest being open; to be read from left to right. Recorded simultaneously by two elastic manometers with transmission by liquid. In both curves the ordinates having the same numbers have the following meaning: 1, the instant preceding the closing of the mitral valve; 2, the opening of the semilunar valve; 3, the beginning of the "dicrotic wave," regarded as marking the instant of closure of the semilunar valve; 4, the instant preceding the opening of the mitral valve (Porter).

transmission, have so far found that the high swift rise at the outset of the systole is soon succeeded by a sudden change. According to them the pressure within the manometer now exhibits fluctuations of greater or less extent which

are due, partly at least, to the inertia of the transmitting liquid; but, with due allowance made for these, the cardiac pressure is seen to maintain itself at a high point throughout most of the systole until the rapid fall begins. During this period of high pressure, the height about which the fluctuations occur may remain nearly the same; or this height may gradually increase, or gradually decrease, up to the beginning of the rapid fall. As is shown by Figure 108, this course of the systolic pressure causes its curve to bend alternately downward and upward between the end of its greatest rise and the beginning of its greatest fall; but between these two points the general direction of the curve approaches the horizontal, and therefore entitles this portion of it to the name of the "systolic plateau." The best of the manometers with air-transmission yields a curve of the pressure within the ventricle which presents a different picture (Figs. 107 and 109). The steeply rising line may diminish
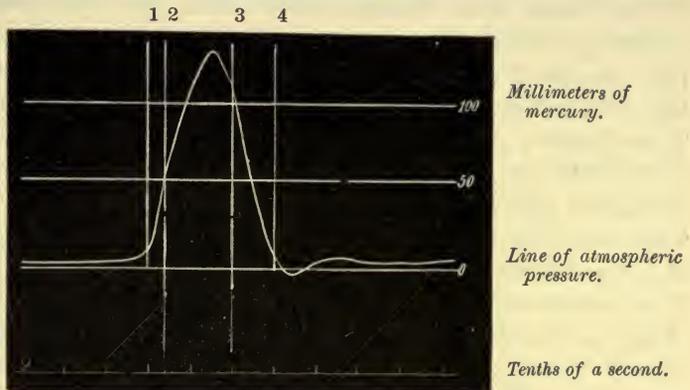
FIG. 109.—Magnified curve of the course of pressure within the left ventricle of the dog, the chest being open; to be read from left to right. Recorded by the elastic manometer with transmission by air. The ordinates have the following meaning: 1, the closure of the mitral valve; 2, the opening of the semilunar valve; 3, the closure of the semilunar valve; 4, the opening of the mitral valve (von Frey).

its steepness somewhat as it ascends, but its rapid turn at the highest point of the curve is succeeded by no plateau. The line simply describes a single peak, and begins the descent which marks the rapid fall of pressure recognized by all observers. In these peaked curves this descent is often steepest in its middle part. Such a peaked curve would indicate, of course, that there is no such thing as the maintenance, during any large part of the systole of the ventricles, of a varying but high pressure. The experienced observer who is the chief defender of the peaked curve holds the plateau to be a product either of too much friction within the manometer tubes, or of a faulty position of the cannula within the heart, whereby communication with the manometer is, for a time, cut off. The able and more numerous adherents of the plateau, on the other hand, attribute the failure to obtain it to the sluggishness of the instrument employed. Recent comparative tests of elastic manometers, and other studies, would seem to show that the curves obtained by liquid transmission, and which exhibit the plateau, afford a truer picture of the general course of the pressure within the ventricles than the peaked curves written by means of air.

The Ventricular Pressure-curve and the Auricular Systole.—It is striking testimony to the smoothness of working of the cardiac mechanism, that the curve of intra-ventricular pressure rarely gives any clear indication of the beginning or end of the auricular systole. This event may be expected to increase the pressure within the ventricles; and, in the curve, the very gentle rise which coincides with the latter and longer part of the ventricular diastole passes into the steep ascent of the commencing ventricular systole by a rounded sweep, which indicates a more rapidly heightened pressure within the ventricle during the auricular systole. As a rule, no angle reveals an instantaneous change of rate to show the beginning or end of the injection of blood by the contracting auricle (see Figs. 107, 108, 109). Occasionally, however, a slight "presystolic" fluctuation of the curve may seem to mark the auricular systole.[1]

The Ventricular Pressure-curve and the Valve-play.—It is also exceedingly striking that no curve, whether it be pointed or show the systolic plateau, gives a clear indication of the instant of the closing or opening of either valve, auriculo-ventricular or arterial (see Figs. 107, 108, 109). These instants, so important for the significance of the curve, can, however, be marked upon it after they have been ascertained indirectly. A method of general application would be as follows: Two elastic manometers are "absolutely graduated" by causing each of them to record a series of pressures already measured by a mercurial manometer. The two elastic manometers can then be made to mark upon the same revolving drum the simultaneous changes of pressure in a ventricle and in its auricle, or in a ventricle and its artery.
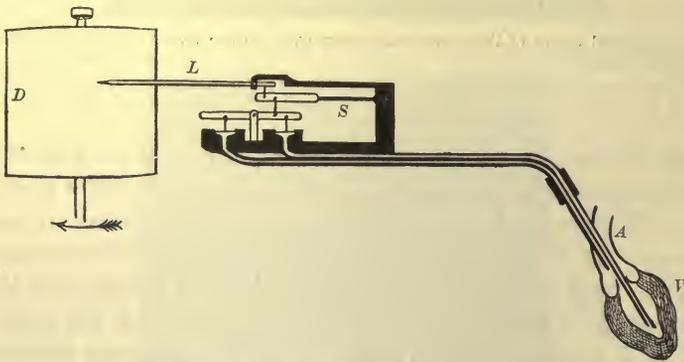
Fig. 110.—Diagram of the differential manometer: *A*, artery: *V*, ventricle; *D*, drum of kymograph, revolving in the direction of the arrow, and covered with smoked paper; *L*, recording lever in contact with the revolving drum; *S*, a spring by which the movement of the lever worked by the disks is transmitted to the recording lever. (The working details of the instrument are suppressed or altered for the sake of clearness.)

The pressure indicated by any point of either curve can then be calculated in terms of millimeters of mercury. That point upon the intra-ventricular curve which marks a rising pressure just higher than the simultaneous pressure in the auricle or artery, may be taken to mark the closing of the cuspid valve

[1] von Frey and Krehl: *Op. cit.*, p. 61.

or the opening of the semilunar valve, as the case may be. By a converse
process, the moment of opening of the cuspid valve, or of closing of the semi-
lunar, may also be ascertained. The practical difficulties in the way of
applying this method to the ventricle and auricle are much greater than to the
ventricle and artery. By another application of the principle just described, a
"differential manometer" has been devised for the purpose of registering as a
single curve the successive differences, from moment to moment, between the
ventricular and auricular pressures, or the ventricular and arterial pressures
(see Fig. 110). To this end, two elastic manometers are fastened immovably
together, and their two elastic disks, instead of bearing upon separate levers,
are made to bear upon a single one, which has its fulcrum between the disks,
and is a lever not of the third order, but of the first, like a common balance.
As the lever or beam of the balance turns from the horizontal as soon as the
scales are pressed upon by unequal weights, so the lever of the differential
manometer turns as soon as the disks are unequally affected by the pressures
within the ventricle and the auricle, or the ventricle and the artery. As, how-
ever, the pressures upon the scales are from above, while those upon the disks
are from below, the disk which tends to "kick the beam" is the one acted
upon by the greater pressure, instead of by the less, as in the case of the scales.
The manometric lever marks its oscillations as a curve upon the kymograph
by the help of a second or "writing lever" connected with it. The persistence
of exactly equal pressures, no matter what their absolute value, in the two
manometers would cause a horizontal line to be drawn by the writing lever.
This would serve as a base-line. The differential manometer is a valuable
instrument, although it is evident that where such minute differences of space
and time are recorded as a curve by such complicated mechanisms, the sources
of error must be numerous and difficult to avoid.[1]

The methods which proceed by the measurement of differences of pressure
may sometimes be controlled, or even replaced, by an easier method, as follows:
If two manometers simultaneously record on the same kymograph the pressure-
curves of the ventricle and the auricle, or of the ventricle and the artery, any
very sudden change of pressure, produced in auricle or artery at the opening or
shutting of a cardiac valve, will produce a peak or angle in the curve of pres-
sure of the auricle or artery. By the rules of the graphic method the point in
the pressure-curve of the ventricle can easily be found which was written at
the same instant with the peak or angle in the auricular or arterial curve.
That point upon the ventricular curve, when marked, will indicate the instant
of opening or shutting of the valve in question. In the pressure-curve ob-
tained from the aorta close to the heart, there is a sudden angle which clearly
marks the instant when the opening of the semilunar valve leads to the sudden
rise of pressure which causes the up-stroke of the pulse (see Fig. 108). Again,
the fluctuation of aortic pressure which we shall learn to know as the "dicrotic
wave" begins at a moment which many believe to follow closely upon the clos-
ure of the semilunar valve. That moment may be indicated by a notch in the

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[1] K. Hürthle: *Pflüger's Archiv für die gesammte Physiologie*, 1891, vol. 49, p. 45.

aortic curve. So, too, the rise of pressure within the auricle produced by its systole may suddenly be succeeded by a fall, the beginning of which must mark the closure of the cuspid valve, which closure thus may correspond with the apex of the auricular curve.

In Figure 108, ordinate 1 indicates the closing, and ordinate 4 the opening, of the mitral valve. These two points were found by help of the differential manometer. Ordinate 2 indicates the opening, and ordinate 3 the closing, of the aortic valve. These two points were marked with the help of the curve of aortic pressure, also shown in Figure 108, each ordinate of which has the same number as the corresponding ordinate of the ventricular curve. In the arterial curve, 2 marks the beginning of the systolic rise, and 3 the beginning of the dicrotic wave, which latter point is treated by the observer as closely corresponding to the closure of the aortic valve. In Figure 109 each ordinate has the same number, and, as regards the valve-play, the same significance, as in Figure 108. Ordinate 1 corresponds to the apex of a peak in the auricular curve (not here given) which represents the end of the auricular systole. Ordinate 2 corresponds to the beginning of the systolic ascent in the aortic curve (not here given). Ordinate 3 was found by comparing, by means of two elastic manometers, the simultaneous pressures in the ventricle and the aorta. Ordinate 4 corresponds, on the auricular pressure-curve, to a point which marks the beginning of a decline of pressure believed by the observer to succeed the opening of the cuspid valve. In both the figures given of the ventricular curve, and in such curves in general, the points which mark the valve-play occur as follows: The closure of the cuspid valve corresponds to a point, not far above the line of atmospheric pressure, where the moderate upward sweep of the ventricular curve takes on the steepness of the systolic ascent. The systole of the auricle is of little force, and the blood injected by it into the distensible ventricle raises the pressure there but little; that little, however, is more than the relaxing auricle presents, and the cuspid valve is closed. Somewhere on the steep systolic ascent occurs the point corresponding to the rise of the ventricular above the arterial pressure, and therefore to the opening of the semi-lunar valve. But other forces beside the arterial pressure must be overcome by the contracting muscle; and the ventricular pressure mounts higher yet, and either stays high for a while, producing the plateau, or, in a peaked curve, at once descends. In either case, not long after the beginning of the sharp descent, the point occurs at which the ventricular pressure falls below the arterial, and the semilunar valve is closed. Beyond this point the curve continues steeply downward, but it is not till a point is reached not far above, or possibly even below, the atmospheric pressure that the pressure in the ventricle falls below that in the auricle, and the cuspid valve is opened.

The Period of Reception, the Period of Ejection, and the Two Periods of Complete Closure of the Ventricle.—During the whole of the period when the cuspid valve is open, the pressure is lower in the ventricle than in the artery; the arterial valve is shut; and blood is entering the ventricle.

This may be called the "period of reception of blood." During the greater part of the period when the cuspid valve is shut, the arterial valve is open; the pressure is higher in the ventricle than in the artery; and the ejection of blood from the former is taking place. This may be called the "period of ejection," and lies in Figures 108 and 109 between the ordinates 2 and 3. The careful work which has enabled us to mark the valve-play upon the ventricular curve has demonstrated the interesting fact that there occur two brief periods during each of which both valves are shut, and the ventricle is a closed cavity. Of these two periods, one immediately precedes the period of ejection, and the other immediately follows it. The first lies, in Figures 108 and 109, between the ordinates 1 and 2; the second, between 3 and 4. The explanation of these two periods is simple. It takes a brief but measurable time for the cardiac muscle, forcibly contracting upon the imprisoned liquid contents of the closed ventricle, to raise the pressure to the high point required to overcome the opposing pressure within the artery and to open the semilunar valve. Again, it takes a measurable time, probably seldom quite so brief as the period just discussed, for the cardiac muscle to relax sufficiently to permit the pressure in the closed ventricle to fall to the low point required for the opening of the cuspid valve. The ventricular cycle, thus studied, falls into four periods: the first is a brief period of complete closure with swiftly rising pressure; the second is the period of ejection, relatively long, and but little variable; the third is a period of complete closure, with swiftly falling pressure; the fourth is the period when the pressure is low and blood is entering the ventricle. This last period is very variable in length, but at the average pulse-rate it is the longest period of all.

Phenomena of the Period of Reception of Blood.—We have already followed the course of the pressure within the ventricle from the moment of opening of the auriculo-ventricular valve to that of its closing (p. 416). During this time the ventricle is receiving its charge of blood, the flaccidity of the wall rendering expansion easy and keeping the pressure low. The blood which enters first has been accumulating in the auricle since the closing of the cuspid valve, and now, upon the opening of this, it both flows and is to some slight degree drawn into the ventricle. This blood is followed by that which, during the remainder of the "repose of the whole heart," moves through the veins and the auricle into the ventricle under the influence of the arterial recoil and the other forces which cause the venous flow (p. 397); and the charge of the ventricle is completed by the blood which is injected at the auricular systole.

The Negative Pressure within the Ventricles.—That the heart, in its diastole, draws something from without into itself is a very ancient belief, and this mode of its working played a great part in the doctrines of Galen and of the Middle Ages. In 1543, Vesalius, who, on anatomical grounds, questioned some of Galen's views as to the cardiac physiology, fully accepted this one.[1]

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[1] *Andreæ Vesalii Bruxellensis, Scholæ medicorum Patavinæ professoris, de Humani corporis fabrica Libri septem.* Basileæ, ex officina Ioannis Oporini, Anno Salutis reparatæ MDXLIII. Page 587.

On the other hand, in 1628, Harvey rejected it. " It is manifest," he says, " that the blood enters the ventricles not by any attraction or dilatation of the heart, but by being thrown into them by the pulses of the auricles."[1] In this particular, modern research in some degree confirms the opinion of the ancients, while denying to suction within the ventricles any such great effect as was once believed in. As a rule, the cuspid valve is not opened till the pressure in the ventricle has fallen to a point not far from the pressure of the atmosphere; it may be even below it. In any case the ventricular pressure usually becomes negative very soon after the opening of the cuspid valve. This negative pressure is of variable extent and continues for a variable time. It is always small as compared with the positive pressure of the systole. Under some circumstances negative pressure may be absent, but it is so very commonly present as certainly to be a normal phenomenon (see Figs. 107, 108, and 109). This negative pressure is revealed by the elastic as well as by the minimum mercurial manometer; it is present in both ventricles; and it is present, to a less degree, even after the chest has been opened, and its aspiration destroyed. It is in virtue of the forces which produce the negative pressure in the manometer that blood is drawn into the heart.

Passing by disproven or improbable theories as to the causes of this suction, we shall find the following statements justified: As the heart lies between the lungs and the chest-wall (including in this term the diaphragm), it is subject, like the chest-wall and the great vessels, to the continuous aspiration produced by the stretched fibres of the elastic lungs. At every inspiration this aspiration is increased by the contraction of the inspiratory muscles. We see, therefore, that the ventricle must overcome this aspiration as part of the resistance to its contraction; and that, as soon as that contraction has ceased, the walls of the ventricle must tend to be drawn asunder by those same forces of elastic recoil in the pulmonary fibres, and of contraction of the muscles of inspiration, which we have seen (p. 387) to produce a slight suction within the great veins in and very near the chest. These same forces produce a slight suction within the ventricles, relaxed in their diastole. But a very slight suction occurs at each ventricular diastole even after the chest has been opened. The causes of this are still obscure; but it is to be borne in mind that the relaxing wall of the ventricle, flabby as it is, possesses some little elasticity, especially at the auriculoventricular ring, and therefore may tend to resume a somewhat different form from that due to its contraction. As the result of this slight elastic recoil, a feeble suction may occur.

N. The Functions of the Auricles.

Connections of the Auricle.—Into the right and left auricles open the systemic and pulmonary veins respectively, and each auricle may justly be regarded as the enlarged termination of that venous system with which it is connected. Until modern times the terms of anatomy reflected this view, and

[1] *Op. cit.*, 1628, p. 26: Willis's translation, Bowie's edition, 1889, p. 28.

from the ancient Greeks to a time later than Harvey, the word " heart " commonly meant the ventricles only, as it still does in the language of the slaughter-house. This termination of the venous system, the auricle, communicates directly with the ventricle, at the auriculo-ventricular ring, by an aperture so wide that, when the cuspid valve is freely open, auricle and ventricle together seem to form but a single chamber.

The Auricle a Feeble Force-pump ; the Pressure of its Systole.—The wall of the auricle is thin and distensible ; it is also muscular and contractile. But the slightest inspection of the dead heart shows how little force can be exerted by the contraction of so thin a sheet of muscle. In the wall of the appendix, however, the muscular structure is more vigorously developed than over the rest of the auricle. The auricle, then, should be a very feeble force-pump ; and such in fact, it is ; for the highest pressure scarcely rises above 20 millimeters of mercury in the right auricle of the dog,[1] and an auricular systole often produces a pressure of only 5 or 10 millimeters.[2] This would be but a small fraction of the maximum ventricular pressure of the same heart. The auricle, however, is equal to its work of completing the filling of the ventricle ; and the feebleness of the auricle will not surprise us when we consider that, at the beginning of its systole, the pressure exerted by the contents of the relaxed ventricle is but little above that of the atmosphere, and offers small resistance to the injection of an additional quantity of blood.

The systole of the auricles is so conspicuous a part of the cardiac cycle when the beating heart is looked at, that its necessity is easily overrated. Even Harvey, in attacking the errors of his day, was led by imperfect methods to estimate too highly the work of the auricular systole (see p. 426). The error, although a gross one, is not rare, of considering the systole of the auricles to be as important for the charging of the ventricles as the systole of the ventricles is for the charging of the arteries. On page 390 the proof has already been given that the work of the heart may entirely suffice to maintain the circulation without aid from any subsidiary source of energy. It must now be added that the ventricles can, for a time, maintain the circulation without the aid of the auricular systole—a clear proof that this systole is not a *sine qua non* for the working of the cardiac pump.

If in an animal, not only anæsthetized but so drugged that all its skeletal muscles are paralyzed, artificial respiration be established and the chest be opened, the circulation continues. If the artificial respiration be suspended for a time, the lungs collapse, asphyxia begins, and the blood accumulates conspicuously in the veins and in the heart. Presently the muscular walls of the auricles may become paralyzed by overdistention, and their systoles may cease, while the ventricles continue at work and may maintain a circulation, although of course an abnormal one. After the renewal of artificial respiration, it may not be till several beats of the ventricles have succeeded,

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[1] Goltz und Gaule: *op. cit.*, p. 106.
[2] W. T. Porter: *op. cit.*, p. 533. S. de Jager: *op. cit.*, p. 506.

without help from the auricles, in unloading the latter and the veins, that the auricles recommence their beats.[1]

On the other hand, it is clear that the auricle is not without importance as a force-pump for completing the filling of the ventricle, even if it can be dispensed with for a time. In curves of the blood-pressure during asphyxia taken simultaneously from the auricle and the ventricle, there may be noted the influence exerted upon the ventricular curve by ineffectiveness of the auricular systole. It is found that, in this case, that slight but accelerated rise of pressure may fail which normally just precedes, and merges itself in, the large swift rise of the ventricular systole. It is found, too, that, under these circumstances, the total height of this systolic rise may be diminished.[2] We shall see presently how, when the pulse becomes very frequent, the importance of the auricular systole may be increased. We have seen already (p. 424) that normally it may probably effect the closure of the cuspid valves.

Time-relations of the Auricular Systole and Diastole.—The auricular systole is not only weak, but brief, being commonly reckoned at about 0.1 of a second (see p. 416). If this be correct for man, at the average pulse-rate of 72 the auricular systole would comprise only about one-eighth of the cycle; would be only one-seventh as long as the auricular diastole; and only about one-third as long as the ventricular systole which immediately follows that of the auricle.

The Auricle a Mechanism for Facilitating the Venous Flow and for the " Quick-charging " of the Ventricle.—Further points in regard to the systole of the auricles can best be treated of incidentally to the general question, What is the principal use of this portion of the heart? The answer is not so obvious as in the case of the ventricles. It may, however, be stated as follows : The auricle is a reservoir, lying at the very door of the ventricle. That door, the cuspid valve, remains shut during the relatively long and unvarying period of the ventricular systole and the brief succeeding period of falling pressure within the ventricle. These periods coincide with the earlier part of the auricular diastole. During all this time the forces which cause the venous flow are delivering blood into the flaccid and distensible reservoir of the auricle, and can thus maintain a continuous flow. But the blood of which the veins are thus relieved during the period of closure of the cuspid valve, accumulates just above that valve to await its opening. When it is opened by the superior auricular pressure, the stored-up blood both flows and is drawn into the ventricle promptly from the adjoining reservoir. From this time on, auricle and ventricle together are converted into a common storehouse for the returning blood during the remainder of the repose of the whole heart, which coincides with the later portion of the long auricular diastole. The next auricular systole completes the charging of the ventricle; and a second use of this systole now becomes apparent, for the sudden transfer by it of blood from auricle to ventricle not only completes the filling of the latter, but

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[1] von Frey und Krehl: *op. cit.*, pp. 49, 59.　G. Colin: *Traité de physiologie comparée des animaux*, Paris, 1888, vol. ii. p. 424.　　　[2] von Frey und Krehl: *op. cit.*, p. 59.

lessens the contents of the auricle, and so prepares it to act as a storehouse during the coming systole of the ventricle. The auricle, then, is an apparatus for the maintenance of as even a flow as possible in the veins and for the rapid and thorough charging of the ventricle. It is clear that, for both uses, the auricle's function as a reservoir is certainly no less important than its function as a force-pump.

The value of a mechanism for the rapid filling of the ventricle increases with the pulse-rate, and with a very frequent pulse must be of great importance, because now time must be saved at the expense of the pause, with its quiet flow of blood through the auricle into the ventricle; and the auricular systole must follow more promptly than before upon the opening of the cuspid valve. If the pulse double in frequency, each cardiac cycle must be completed in one-half the former time; but we have seen that the ventricle requires for its systole a time which cannot be shortened with the cycle to the same degree as can its diastole. Of heightened value now to the ventricle will be the adjoining reservoir, which is filling while the cuspid valve remains closed, and from which, as soon as that valve is opened, the necessary supply not only flows, but is sucked and pumped into the ventricle, for, when increased demands are made upon the heart, the usefulness of an increased frequency of beat disappears if the volume transferred at each beat from veins to arteries diminish in the same proportion as the frequency increases. No increase of the capillary stream can then follow the more frequent strokes of the pump.[1]

Negative Pressure within the Auricle; its Probable Usefulness.—The course of the pressure-curve of the auricle, as shown by the elastic manometer, is too complex and variable, and its details are too much disputed, for it to be given here. But certain facts regarding the auricular pressure are of much interest in connection with the use of the auricle which has just been discussed. Once, and perhaps oftener, in each cycle, the pressure in the auricle may become negative, perhaps to the degree of from -2 to -10 millimeters of mercury even in the open chest,[2] and of course becomes still more so when the latter is intact, sinking in this case to perhaps -11.2 millimeters.[3] What is striking in connection with the "quick-charging" of the ventricle is that the greatest and longest negative pressure in the auricle coincides, as we should expect, with the earlier part of its diastole, and therefore with the systole of the ventricle, when the auricle is cut off from it by the shut valve.[4] By this suction within the auricle the flow from the veins into it probably is heightened, and the store of blood increased which accumulates in the reservoir to await the opening of the valve. The quick-charging mechanism itself is quickly charged. Nor should it be forgotten that the work of the ventricle contributes in some degree to this suction within the auricle. The heart is air-tight in the chest, which is a more or less rigid case. At each ventricular

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[1] von Frey und Krehl: *op. cit.*, p. 61.
[2] de Jager: *op. cit.*, p. 507. W. T. Porter: *op. cit.*, p. 533.
[3] Goltz und Gaule: *op. cit.*, p. 109.
[4] von Frey und Krehl, *op. cit.*, p. 53. Porter, *op. cit.*, p. 523.

systole the heart pumps some blood out of this case, and shrinks as it does so, thus tending to produce a vacuum; in other words, to increase the amount of negative pressure within the chest, and thus help to expand the swelling auricles. Therefore for the suction which helps to charge the auricles during the systole of the ventricles, that systole itself is partly responsible.[1]

Is the Auricle Emptied by its Systole ?—Authorities differ still as to the extent to which the auricle is emptied by its systole; some holding the scarcely probable view that, during this time, its contents are all, or nearly all, transferred to the ventricle;[2] and others taking the widely different view that the auricle actually continues to receive blood during its systole, which latter simply increases the discharge into the ventricle. According to this latter opinion the flow from the great veins into the auricle is absolutely unbroken.[3] All are agreed, however, that the auricular appendix is the most completely emptied portion of the chamber.

Are the Venous Openings into the Auricle closed during its Systole ? If not, does Blood then regurgitate, or enter ?—As to these questions differences of opinion are possible, because at the openings of the veins into the auricle no valves exist which are effective in the adult, except at the mouth of the coronary sinus. It is therefore a question, what happens at the mouths of the veins during the auricular systole. These mouths are surrounded by rings composed of the muscular fibres of the auricular wall; and for some distance from the heart the walls of some of the great veins are rich in circular fibres of muscle. We have seen already (p. 407) that a rhythmic contraction of the venæ cavæ and pulmonary veins occurs just before the systole of the auricles and must accelerate the flow into the latter. Their swiftly following systole is known to begin at the mouths of the great veins and from these to spread over the rest of each auricle. It is evident at once that the circular fibres must either narrow or obliterate, like sphincters, the mouths of the veins at the outset of the systole, and that these fibres thus take the place of valves. If the closure be complete, all the blood ejected by the systole must enter the ventricle, and a momentary standstill of blood and rise of pressure in the veins just without the auricle must accompany its brief systole. A recent observer believes the flow into the auricle to be interrupted even more than once during its cycle.[4] If the venous openings be not closed but only narrowed during the systole of the auricles, the transfer of all or most of the ejected blood to the ventricle must depend upon the pressure being lower therein than at the venous openings. A slight regurgitation into the veins would, like the complete closing of their mouths, cause a momentary checking of their blood-flow just without the auricle, and a slight rise of pressure. Such a checking of the flow has in some

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[1] A. Mosso: *Die Diagnostik des Pulses*, etc. Zweiter Theil: Ueber den negativen Puls, p. 42.

[2] M. Foster: *A Text-book of Physiology*, New York, 1895, p. 182.

[3] Skoda: "Ueber die Function der Vorkammern des Herzens," *Sitzungsberichte der mathem.-naturw. Classe der kais. Akademie der Wissenschaften in Wien*, 1852, vol. ix. p. 788. L. Hermann: *Lehrbuch der Physiologie*, 1892, p. 66.   [4] W. T. Porter: *Op. cit.*, p. 534.

cases been observed and ascribed to regurgitation.[1] A systolic narrowing without closure of the venous mouths would leave room also for the view already given, that so far is regurgitation from taking place, that even during the systole of the auricles blood enters them incessantly, and the venous flow is never checked. In this case the systole of the auricle would still empty it partially into the ventricle, owing to the lowness of the pressure there.

The time has not arrived for a decision as to all these questions, which are surrounded by practical difficulties; but fortunately they do not throw doubt upon the functions of the auricle as a reservoir and pump which may be swiftly filled, and may swiftly complete the filling of the ventricle which it adjoins.

O. The Arterial Pulse.

Nature and Importance.—The expression " arterial pulse " is restricted commonly to those incessant fluctuations of the arterial pressure which correspond with the incessant beatings of the ventricles of the heart. These rhythmic fluctuations of the arterial pressure have been explained already (p. 385) to depend upon the rhythmic intermittent injections of blood from the ventricles; upon the resistance to these injections produced by the friction within the blood-vessels; and upon the elasticity of the arterial walls. It has also been explained that the interaction of these three factors is such that the blood, in traversing the capillaries, comes to exert a continuous pressure, free from rhythmic fluctuations; in other words, that the pulse undergoes extinction at the confines of the arterial system. It is at once apparent that the pulse may be affected by an abnormal change, either in the heart's beat, in the elasticity of the arteries, or in the peripheral resistance, or by a combination of such changes; and that, therefore, the characters of the pulse possess an importance in medical diagnosis which justifies a brief further discussion of them.

A pulsating artery not only expands, but is lengthened. The sudden increase in the contents of an artery which causes the pulse therein, is accommodated not merely by the increase of calibre which produces the " up-stroke " of the arterial wall against the finger, but also by an increase in the length of the elastic vessel. If the artery be sinuous in its course, this increase in length suddenly exaggerates the curves of the vessel, and thus produces a slight wriggling movement. This is sometimes very clearly visible in the temporal arteries of emaciated persons. On the other hand, the increase in the calibre of the artery is relatively so slight that it is invisible at the profile even of a large artery, dissected clean for a short distance for the purpose of tying it. Such a vessel appears pulseless to the eye, although its pulse is easily felt by the finger, which slightly flattens the artery and thus gains a larger surface of contact.

Transmission of the Pulse.—If an observer feel his own pulse, placing

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[1] François-Franck: " Variations de la vitesse du sang dans les veines sous l'influence de la systole de l'oreillette droite," *Archives de physiologie normale et pathologique*, 1890, p. 347.

the finger of one hand upon the common carotid artery, and that of the other upon the dorsal artery of the foot at the instep, he will perceive that the pulse corresponding to a given heart-beat occurs later in the foot than in the neck. This phenomenon is readily comprehended by considering that room for the "pulse-volume" injected by the heart is made in the root of the arterial system both by local expansion and by a more rapid displacement of blood into the next arterial segment. This next segment, in turn, accommodates its increased charge by local expansion and by a more rapid displacement; and this same process involves segment after segment in succession, onward toward the capillaries. The expansion of the arterial system, then, is a progressive one, and, as the phrase is, spreads as a wave from the aorta onward to the arterioles. The rate of transmission of the "pulse-wave" from a point near the heart to one remote from it, may be calculated. This is done by comparing the time which elapses between the occurrence of the up-stroke of the pulse in the nearer and in the farther artery with the distance along the arterial system which separates the two points of observation. In one case, for example, that of an adult, the absolute amount of the postponement of the pulse— that is, the time required for the transmission of the pulse-wave from the heart itself to the *arteria dorsalis pedis*, was 0.193 second.[1] The time of transmission of the pulse-wave from the heart to the *dorsalis pedis* is often longer than in this case, amounting to 0.2 second or a little more. If we reckon the duration of the ventricular systole at about 0.3 second, it is evident that the fact of the postponement of the pulse in the arteries distant from the heart does not invalidate the general statement that the arterial pulse is synchronous with the systole of the ventricles.

The general estimates of the rate, as opposed to the absolute time, of transmission of the pulse-wave vary, in different cases, from more than 3 meters to more than 9 meters per second. As the blood in the arteries does not pass onward at a swifter rate than about 0.5 meter per second, it is clear that the wave of expansion moves along the artery many times faster than the blood does; and that to confound the travelling of the wave with the travelling of the blood would be a very serious error, easily avoided by bearing in mind the causes of the pulse-wave as already given.

Investigation by the Finger.—The feeling of the pulse has been a valuable and constantly used means of diagnosis since ancient times. Indeed, the ancient medicine attached to it more importance than does the practice of to-day. But it is still advisable to warn the beginner that he may not look to the pulse for "pathognomonic" information; that is to say, he may not expect to diagnosticate a disease solely by touching an artery of the patient under examination. The pulse is most commonly felt in the radial artery, which is convenient, superficial, and well supported against an examining finger by the underlying bone. Many other arteries, however, may be utilized.

Frequency and Regularity.—The most conspicuous qualities of the pulse

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[1] J. N. Czermak: *Gesammelte Schriften*, 1879, Bd. i. Abth. 2, p. 711.

are frequency and regularity. Usually these can be appreciated not merely by a physician but by any intelligent person. The physiological variations in the frequency of the heart's beats have been referred to already (p. 412). In an intermittent pulse the rhythm is usually regular, but, at longer or shorter intervals, the ventricle omits a systole, and therefore, the pulse omits an up-stroke. Either intermittence or irregularity of the cardiac beats may be caused by transient disorder as well as by serious disease.

Tension.—When unusual force is required in order to extinguish the pulse by compressing the artery against the bone, the arterial wall, and hence the pulse, is said to possess high tension, or the pulse is called incompressible, or hard. Conversely, the pulse is said to be of low tension, compressible, or soft, when its obliteration is unusually easy. A very hard pulse is sometimes called "wiry;" a very soft one, "gaseous." High tension, hardness, incompressibility, obviously are directly indicative of a high blood-pressure in the artery; and the converse qualities of a low pressure. It follows from what has gone before that the causes of changes in the arterial pressure, and hence in the tension, may be found in changes either in the heart's action, or in the peripheral resistance, or, as is very common, in both. An instrument called the sphygmomanometer[1] is sometimes applied to the skin over an artery, in order to obtain a better measurement of its hardness or softness than the finger can make. This instrument is not free from sources of error.

Size.—When the artery is unusually increased in calibre at each up-stroke of the pulse, the pulse is said to be large. When, at the up-stroke, the calibre changes but little, the pulse is said to be small. A very large pulse is sometimes called "bounding;" a very small one, "thready." Largeness of the pulse must be distinguished carefully from largeness of the artery. The former phrase means that the fluctuating part of the arterial pressure is large in proportion to the mean pressure. But if the mean pressure be great while the fluctuating part of the pressure is relatively small, the artery, even at the end of the down-stroke, will be of large calibre, while the pulse will be small.

It has been seen that the increased charge of blood which an artery receives at the ventricular systole is accommodated partly by increased displacement of blood toward the capillaries, and partly by that increase in the capacity of the artery which is accompanied by the up-stroke of the pulse. The less the contents of the artery the less is the arterial pressure, the less the tension of the wall, and the more yielding is that wall. The more yielding the wall, the more of the increased charge of blood does the artery accommodate by an increase of capacity and the less by an increase of displacement. Therefore, a large pulse often accompanies a low mean pressure in the arteries, and hence may appear as a symptom after large losses of blood. In former days, when bloodletting was practised as a remedial measure, imperfect knowledge of the mechanics of the circulation sometimes caused life to be endangered; for a "throbbing" pulse in a patient who had been bled already was liable to be taken as an "in-

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[1] From σφυγμός, pulse.

dication" for the letting of more blood. If this were done, an effect was combated by repeating its cause.[1]

Celerity of Stroke.—When each up-stroke of the pulse appears to be slowly accomplished, requiring a relatively long interval of time, the pulse is called slow, or long. When each up-stroke appears to be quickly accomplished, requiring a relatively short time, the pulse is called quick or short. These contrasted qualities are among the most obscure of those which the skilled touch is called upon to appreciate.

The Pulse-trace.—The rise and fall of a pulsating human artery, if near enough to the skin, may be made to raise and lower the recording lever of a somewhat complicated instrument called a sphygmograph.[2] Of this instrument a number of varieties are in use. If the fine point of the lever be kept in contact with a piece of smoked paper which is in uniform motion, a "pulse-trace" or "pulse-curve" is inscribed, which shows successive fluctuations, larger and smaller, which tend to be rhythmically repeated, and which depend upon the movements of the arterial wall produced by the fluctuations of blood-pressure. In an animal, a manometer may be connected with the interior of an artery, and thus the fluctuations of the blood-pressure may be observed more directly. It has been explained (p. 382) that the mercurial manometer is of no value for the study of the finer characters of the pulse, owing to the inertia of the mercury. On the other hand, the best forms of elastic manometer give pulse-traces which are more reliable than those of the sphygmograph. This is because the sphygmographic trace is subject to unavoidable errors dependent upon the physical qualities of the skin and other parts which intervene between the instrument and the cavity of the artery. Nevertheless, the sphygmographic pulse-trace, or "sphygmogram," is the only pulse-trace which can be obtained from the human subject; and, when obtained from an animal, it has so much in common with the trace recorded by the elastic manometer, that the sphygmograph has been much used for the study of the human pulse, in health and disease, both by physiologists and by medical practitioners. As a means of diagnosis, however, the sphygmogram still leaves much to be desired. The same instrument, applied in immediate succession to different arteries of the same person, gives, as might be expected, pulse-traces of somewhat different forms. The same artery of the same person yields to the same instrument at different times different forms of trace, depending upon different physiological states of the circulation. But the same artery yields traces of different form to sphygmographs of different varieties applied to it in immediate succession; and even moderate changes in adjustment cause differences in the form of the successive traces which the same instrument obtains from the same artery. It is no wonder, therefore, that great care must be exercised in comparing sphygmographic observations, and in drawing general conclusions from the information which they impart.

The Details of the Sphygmogram.—Figure 111 is a fair example of

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[1] Marshall Hall: *Researches principally relative to the Morbid and Curative Effects of Loss of Blood*, London, 1830.　　　　[2] From σφυγμός, pulse, and γράφειν, to record.

the sphygmograms commonly obtained from the healthy human radial pulse. When this trace was taken, the subject's heart was beating from 58 to 60 times

FIG. 111.—Sphygmogram from a normal human radial pulse beating from 58 to 60 times a minute. To be read from left to right (Burdon-Sanderson).

a minute. The trace records the effects upon the lever of five successive complete pulsations of the artery, which all agree in the general character of their details, while differing in minor respects. By the tracing of each pulsation the up-stroke is shown to be sudden, brief, and steady, while the down-stroke is gradual, protracted, and oscillating. The commencing recoil of the arterial wall succeeds its expansion with some suddenness. In many sphygmograms this is exaggerated by the inertia of the instrument. As shown by the trace represented in the figure, and by most such traces, the recoil soon changes from rapid to gradual, and, in the trace, its protracted line becomes wavy, indicating that the slow diminution of calibre varies its rate, or even is interrupted by one or more slight expansions, before it reaches its lowest, and is succeeded by the up-stroke of the next pulsation. In each of the five successive pulsations the traces of which are shown in Figure 111, the line which represents the more gradual portion of the down-stroke of the pulse is made up of three waves, of which the first is the shortest, the last the longest and lowest, and the middle one intermediate in length, but by far the highest. This middle wave is, in fact, the only one of the three to produce which an actual rise of pressure occurs; in each of the other two, no rise, but only a diminished rate of decline, is exhibited. The changes of pressure which produce the first and third of the waves just spoken of, in the pulse-trace under consideration, are very obscure in their origin, and are inconstant in their occurrence, sometimes being more numerous than in the trace shown in Figure 111, and sometimes failing altogether to appear.

The Dicrotic Wave.—The oscillation of pressure, however, which produces the middle wave of each of the pulsations of Figure 111, is so constant in its occurrence that it is undoubtedly a normal and important phenomenon, although, in different sphygmograms, the height, and position in the trace, of the wave inscribed by this oscillation may vary. Occasionally this oscillation is morbidly exaggerated, so that it may be not only recorded by the sphygmograph, but even felt by the finger, as a second usually smaller up-stroke of the pulse. In such a case the artery is felt to beat twice at each single beat of the ventricle, and is said, technically, to show a "dicrotic"[1] pulse. Where a dicrotic pulse can be detected by the finger, it is apt to accompany a markedly low mean tension of the arterial wall. The dicrotic pulse was known, and named, long before the sphygmograph revealed the fact that the pulse is always dicrotic, although to a degree normally too slight for the finger to

[1] From δίκροτος, double-beating.

appreciate. The sphygmographic wave which records the slight "dicrotism" of the normal pulse is called the "dicrotic wave." Where dicrotism can be felt by the finger, the sphygmogram naturally exhibits a very conspicuous dicrotic wave.

The origin of the dicrotic oscillation has been much discussed, and is not yet thoroughly settled, important as a complete settlement of it would be to the true interpretation and clinical usefulness of the sphygmogram. It is believed by some that this fluctuation of pressure is produced at the smaller arterial branches, as a reflection of the main pulse-wave, and that the dicrotic wave, thus reflected, travels toward the heart, and, naturally, reaches a given artery after the main wave of the pulse has passed over it, travelling in the opposite direction. The weight of opinion and of probability, however, is in favor of the view that the dicrotic wave essentially depends upon a slight rise of the arterial pressure, or slackening of its decline, due to the closing of the semilunar valve; and that, therefore, this wave follows the main wave of arterial expansion outward from the heart, instead of being reflected inward from the periphery. If the dicrotic wave be caused solely by reflection from the periphery, it ought, in a sphygmogram from a peripheral artery, to begin at a point nearer to the highest point of each pulsation than in the case of an artery near the heart, in which latter vessel, naturally, a reflected wave would undergo postponement. On the other hand, if the dicrotic wave be transmitted toward the periphery, and caused solely by the closure of the aortic valve, it ought, in a sphygmogram from a peripheral artery, to occupy very nearly the same relative position as in a sphygmogram taken from an artery near the heart. But a wave running toward the periphery may be modified by a reflected wave in the same vessel, and a reflected wave may undergo a second reflection at the closed aortic valve, or even elsewhere, and thus give rise to an oscillation which will be transmitted toward the periphery. These statements show with what technical difficulties the subject is beset, whether the sphygmograph be employed, or, in the case of animals, the elastic manometer, the traces recorded by which also exhibit the dicrotic wave. As already stated, however, the probabilities are in favor of the valvular origin of the dicrotic wave.

If it be true that the closure of the aortic valve causes the dicrotic wave, the instant marked by the commencement of this wave, in the manometric trace inscribed by the pressure within the first part of the arch of the aorta itself, practically marks the instant of closure of the aortic valve. We have seen (p. 422) that this doctrine has been made use of in the elucidation of the curve of the pressure within the ventricle.

The Diagnostic Limitations of the Sphygmogram.—The feeling of the pulse, imperfect as is the most skilled touch, cannot be replaced by the use of the sphygmograph. The presence, between the cavity of the artery and the surface of the body, of a quantity of tissue the amount and elasticity of which differ in different people, and even differ over neighboring points of the same artery, renders it impossible so to adjust the spring of the sphygmo-

graph as to be able to obtain a reliable base-line corresponding to the abscissa, or line of atmospheric pressure, in the case of the manometric curve of blood-pressure. The effects produced by slight differences in the placing of the instrument tend to the same result. By the absence of such a base-line the sphygmographic curve is shorn of quantitative value as a curve of blood-pressure, and cannot give information as to whether, in clinical language, the pulse be hard or soft, large or small. Nor can a long or short pulse be identified from the appearance of the sphygmogram.[1] The pulse-trace still requires much elucidation ; but when further study shall have rendered clearer the true extent, the normal variations, and the causes of the complex and incessant oscillations of the walls of the arteries, it may well be believed that both physiology and practical medicine will have gained an important insight into the laws of the circulation of the blood.

P. The Movement of the Lymph.

The Lymphatic System.—The lymph is contained within the so-called lymphatic system, the nature of which may be summarized as follows :

The lymph appears first in innumerable minute irregular gaps in the tissues, which gaps communicate in various ways with one another, and with minute lymphatic vessels, which latter, when traced onward from their beginnings, presently assume a structure comparable to that of narrow veins with very delicate walls and extremely numerous valves. These valves open away from the gaps of the tissues, as the valves of the veins open away from the capillaries. The lymphatic vessels unite to form somewhat larger ones, each of which, however, is of small calibre as compared with a vein of medium size, until at length the entire system of vessels ends, by numerous openings, in two main trunks of very unequal importance, the thoracic duct and the right lymphatic duct. The latter is exceedingly short, and receives the terminations of the lymphatics of a very limited portion of the body ; the terminations of all the rest, including the lymphatics of the alimentary canal, are received by the thoracic duct, which runs the whole length of the chest. Both of the main ducts have walls which, relatively, are very thin ; and, like the smaller lymphatics, the ducts are abundantly provided with valves so disposed as to prevent any regurgitation of lymph from either duct into its branches. Each duct terminates on one side of the root of the neck, where, in man, the cavity of the duct joins by an open mouth the confluence of the internal jugular and subclavian veins where they form the innominate vein. At the opening of each duct into the vein a valve exists, which permits the free entrance of lymph into the vein, but forbids the entrance of blood into the duct.

It is a peculiarity of the lymphatic system that some of its vessels end and begin by open mouths in the so-called serous cavities of the body—those vast irregular interstices between organs the membranous walls of which interstices are known as the peritoneum, the pleuræ, and the like. For present purposes,

[1] M. von Frey : *Die Untersuchung des Pulses*, 1892, p. 35.

therefore, these serous cavities may be regarded as vast local expansions of portions of the lymph-path. Another peculiarity of the lymphatic system depends upon the presence of the lymphatic glands or ganglia, which also are intercalated here and there between the mouths of lymphatic vessels which enter and leave them. The nature and importance of these bodies have been dealt with in dealing with the origin of the leucocytes and the nature of the lymph (p. 345). For the present purposes the ganglia are of interest in this, that the lymph which traverses their texture meets, in so doing, with much resistance from friction. Physiologically, therefore, the lymph-path as a whole, extending from the tissue-gaps to the veins at the root of the neck, both differs from, and in some respects resembles, the blood-path from the capillaries to the same point.

The origin of the lymph has been discussed already (p. 362), and has been found to be partly from the blood in the capillaries, and partly from the tissues, to say nothing of the products directly absorbed from the alimentary canal during digestion. The quantity of material which leaves the lymph-path and enters the blood during twenty-four hours is undoubtedly large, amounting, in the dog, to about sixty cubic centimeters for each kilogram of body-weight. The movement of the lymph is, therefore, of physiological importance ; and the causes of this movement must now be considered.

Absence of Lymph-hearts.—It is a striking fact that, in man and the other mammals, there exist no " lymph-hearts " for the maintenance of the lymphatic flow. Unstriped muscular fibres, indeed, exist in the walls of the lymphatics ; and rhythmical variations in the calibre of some of these have been described. It remains doubtful, however, whether these variations, when present, are produced by muscular contractions in the walls of the lymphatics, or whether the muscular fibres exist in these, as in the blood-vessels, rather for the regulation of their calibre than for the propulsion of their contents. It is not improbable that the muscular fibres of the walls of the lymphatics further resemble those of the blood-vessels in being under the control of the nervous system; and it has been shown that, in the splanchnic nerve of the dog, there exist centrifugal fibres, stimulation of which produces dilatation of the *receptaculum chyli*.[1]

Differences of Pressure.—The fundamental causes of the movement of the lymph are, that at the beginning of its path in the gaps of the tissues it is under considerable pressure ; that at the end of its path at the veins of the neck it is under very low pressure, which often, if not usually, is negative ; and that, throughout the lymph-path, the valves are so numerous as to work effectively against regurgitation. The pressure of the lymph in the gaps of the tissues has been estimated at one half, or more, of the capillary blood-pressure,[2] which latter has been stated (p. 376) to be from 24 to 54 millimeters

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[1] L. Camus et E. Gley: "Recherches expérimentales sur les nerfs des vaisseaux lymphatiques," *Archives de physiologie normale et pathologique*, 1894, p. 454.

[2] A. Landerer: *Die Gewebsspannung in ihrem Einfluss auf die örtliche Blut- und Lymphbewegung*, Leipzig, 1884, p. 103.

of mercury. The difference between one half of either of these pressures and the pressure in the veins of the neck, which pressure is not far from zero, is quite enough to produce a flow from the one point to the other. To this flow a resistance is caused by the friction along the lymph-path, which resistance causes the lymph to accumulate in the gaps of the tissues, and the pressure there to rise, until the tension of the tissues resists further accumulation more forcibly than friction resists the onward movement of the lymph. The little-known forces which continually produce fresh lymph, and pour it into the tissue-gaps against resistance, cannot be discussed here further than has been done in treating of the origin of the lymph (p. 362).

Thoracic Aspiration.—The causes have already been stated fully of that low, perhaps negative, pressure in the veins at the root of the neck which renders possible the continuous discharge of the lymph into the blood (p. 387). It need only be noted here that when inspiration rhythmically produces, or heightens, the suction of blood into the chest, it must also produce, or heighten, the suction of lymph out of the mouths of the thoracic and right lymphatic ducts. Moreover, as the thoracic duct lies with most of its length within the chest, each expansion of the chest must tend to expand the main part of the duct, and thus to suck into it lymph from the numerous lymphatics which join the duct from without the chest; while the numerous valves in the duct must promptly check any tendency to regurgitation from the neck.

The Bodily Movements and the Valves.—Like the flow of the blood in the veins, the flow of the lymph in its vessels is powerfully assisted by the pressure exerted upon the thin-walled lymphatics by the contractions of the skeletal muscles; for the very numerous valves of the lymphatics render it impossible for the lymph to be pressed along them by this means in any other than the physiological direction toward the venous system. Experiment shows that even passive bending and straightening of a limb in which the muscles remain relaxed, increases to a very great extent the discharge of lymph from a divided lymphatic vessel of that limb. It is probable, therefore, that movement in any external or internal part of the body, however produced, tends to relieve the tension in the tissues by pressing the lymph along its path.

Conclusion.—The movement of the lymph produced in these various ways is doubtless irregular; but a substance in solution, injected into the blood, can be identified in the lymph collected from an opening in the thoracic duct at the neck in from four to seven minutes after the injection.[1] The physiological importance of the lymph-movement is shown not only by the large amount of matter which daily leaves the lymphatic system to join the blood, but also by the evil effects which result from an undue accumulation of lymph, more or less changed in character, in the gaps of the tissues. Such an accumulation constitutes dropsy. It may occur in a serous cavity or in the subcutaneous tissue; in the latter case giving rise to a peculiar swelling which "pits on

[1] S. Tschirwinsky: "Zur Frage über die Schnelligkeit des Lymphstromes und der Lymph-filtration," *Centralblatt für Physiologie*, 1895, Band ix. p. 49.

pressure." Any tissue the meshes of which are thus engorged with lymph is said to be " œdematous." [1]

PART II.—THE INNERVATION OF THE HEART.

It has long been known that the frog's heart can be kept beating for many hours after its removal from the body. In 1881, Martin [2] succeeded in maintaining the beat of the dog's heart after its complete isolation from the central nervous system and the systemic blood-vessels. Ludwig and his pupils [3] have attained the same result in a different way. In 1895, Langendorff [4] was able by circulating warmed oxygenated, defibrinated blood through the coronary vessels to maintain the hearts of rabbits, cats, and dogs in activity after their total extirpation from the body. It is evident, therefore, that the cause of the rhythmic beat of the heart lies within the heart itself, and not within the central nervous system.

Cause of Rhythmic Beat.—It has been much disputed whether the cardiac muscle possesses the power of rhythmical contraction or whether the rhythmic beat is due to the periodic stimulation of the muscle by the discharge of nerve-impulses from the ganglion-cells of the heart. The arrangement of the ganglion-cells and nerves suggests the latter view.

The Intracardiac Ganglion-cells and Nerves.—In the frog the cardiac nerves, arise by a single branch from each vagus trunk and run along the great veins through the wall of the sinus venosus, where many ganglion-cells are found, [5] to the auricular septum. Here they unite in a strong plexus richly provided with ganglion-cells. [6] Two nerves of unequal length and thickness leave this plexus and pass along the borders of the septum to the auriculo-ventricular junction, where each enters a conspicuous mass of cells known as Bidder's ganglion. [7] Ventricular nerves spring from these ganglia and can be followed with the unaided eye some distance on the ventricle. With the chloride-of-gold method, the methylene-blue stain, and especially the nitrate-of-silver impregnation, the ventricular nerves can be traced to their termination. Some difference of opinion exists regarding the manner of their distribution and the precise nature of their terminal organs. The following facts, however, may be considered established both for the batrachian and the mammalian heart. [8]

The ventricular nerves form a rich plexus beneath the pericardium and endocardium. Branches from these plexuses form a third plexus in the myocardium or heart muscle, from which arise a vast number of non-medullated

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[1] From οἴδημα, a swelling.   [2] Martin, 1881, p. 119.

[3] Stolnikow, 1886, p. 2; Pawlow, 1887, p. 452.

[4] Langendorff, 1895, p. 293; also Martin and Applegarth, 1890, p. 275; Arnaud, 1891, p. 396; Hédon and Gilis, 1892, p. 760; Porter, 1896, p. 39.   [5] Remak, 1844, p. 463.

[6] Ludwig, 1848, p. 140.   [7] Bidder, 1852, p. 169.

[8] The literature of this subject has been collected by Jacques (1894, p. 622; and 1896, p. 517) and by Heymans and Demoor (1895, p. 619). For the development of the cardiac nervous system in different classes of vertebrates, see His, Jr., 1891, pp. 1–64; compare His and Romberg, 1890, pp. 374 and 416.

terminal nerves, enveloping the muscle-fibres and ending in small enlargements or nodosities of various forms. Similar " varicose " enlargements are observed along the course of the nerves. The nerve-endings are in contact with the naked muscle-substance, the mode of termination resembling in general that observed in non-striated muscle. Ganglion-cells are found chiefly in the auricular septum and the auriculo-ventricular furrow, but are present also beneath the pericardium of the upper half of the ventricle. No ganglia have as yet been satisfactorily demonstrated within the apical half of the ventricle, and most observers do not admit their presence within the ventricular muscle itself.[1] The nerve-cells are unipolar, bipolar, or multipolar.

Certain unipolar cells in the frog are distinguished by a spherical form, a pericellular network, and two processes—namely, the axis-cylinder or straight process, and the spiral process. The latter is wound in spiral fashion about the axis-cylinder, ending in the pericellular net. According to Retzius and others, the spiral is not really a process of the cell, but arises in a distant extra-cardiac cell and carries to the heart-cell a nervous impulse which is transmitted from the spiral process to the cell by means of the contact between the pericellular net and the cell-body. Section of the cardiac fibres of the vagus causes the spiral " process " and pericellular net to degenerate, the cell-body and axis-cylinder process remaining untouched, showing that the spiral process is the terminal of a nerve-fibre running in the vagus trunk.[2]

Nerve-theory of Heart-beat.—The theory of the nervous origin of the heart-beat rests in part on the correspondence between the degree of contractility of the various parts of the heart and the number of nerve-cells present in them. Thus the power of rhythmical contraction is greater in the auricle, in which there are many cells, than in the ventricle, in which there are fewer. The properties of the apical half, or " apex," of the ventricle are considered to be of especial importance in the study of this problem, because the apex, as has been said, is believed to contain no ganglion-cells. This part of the ventricle stops beating when separated from the heart, while the auricles and the ventricular stump continue to beat. The apex need not be cut away in order to isolate it. By ligating[3] or squeezing the frog's ventricle across the middle with a pair of forceps the tissues at the junction of the upper and the lower half of the ventricle can be crushed to the point at which physiological connection is destroyed but physical continuity still preserved.[4] Such frogs have been kept alive as long as six weeks. The apex does not as a rule beat again.[5] The exceptions can be explained as the consequence of accidental stimulation. The conclusion drawn is that the apex, in which ganglion-cells have not been satisfactorily demonstrated, has not the power of spontaneous pulsation which

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[1] For contrary opinion see Tumänzew and Dogiel, 1890, p. 494, and Berkeley, 1894, p. 90; also the very beautiful plates of Lee, 1849, p. 43, showing subpericardial nerves and ganglia (?) in the calf's heart.

[2] Nikolajew, 1893, p. 73.   [3] Heidenhain, 1854, p. 47.

[4] Bernstein, 1876, p. 386; Bowditch, 1879, p. 105.

[5] Bowditch, 1871, p. 169; Merunowicz, 1875, p. 132; Bernstein, 1876, pp. 386, 435; Bowditch, 1879, p. 104; Aubert, 1881, p. 362; Ludwig and Luchsinger, 1881, p. 231; Langendorff, 1884, p. 6.

distinguishes the remainder of the heart. This view is further supported by the observation that a slight stimulus applied to the base of a resting ventricle will often provoke a series of contractions, while the same stimulus applied to the apex will cause but a single contraction.[1]

The action of muscarin on the heart is often held to indicate the nervous origin of the heart-beat. Muscarin arrests the heart of the frog and other vertebrates, but has no similar action on any other muscle either striped or smooth, nor does it arrest the heart of insects and mollusks. It follows that muscarin does not cause arrest by acting directly upon the contractile material of the heart. The contractile material being excluded, the assumption of a nervous mechanism on the integrity of which the heart-beat depends seems necessary to explain the effect of the poison.[2]

Further arguments are based on uncertain analogies between the heart and other rhythmically contracting organs.

Muscular Theory of Heart-beat.—The evidence just stated cannot be regarded as proof of the nervous origin of the heart-beat. The most that can be claimed is that it makes such a conception plausible. Even this claim has been denied by not a few investigators who believe that the heart-beat is a purely muscular phenomenon. Here again the properties of the apex are considered to be of the first importance. It has been shown that a strip of muscle cut from the apex of the tortoise ventricle and suspended in a moist chamber begins in a few hours to beat apparently of its own accord with a regular but slow rhythm, which has been seen to continue as long as thirty hours. If the strip is cut into pieces and placed on moistened glass slides each piece will contract rhythmically.[3] Yet in the apex of the heart no nerve-cells have been found.

The apex of the batrachian heart will beat rhythmically in response to a constant stimulus. Thus if the apex is suspended in normal saline solution and a constant electrical current kept passing through it, beats will appear after a time, the frequency of pulsation increasing with the strength of the current.[4] Very strong currents cause tonic contraction. An apex made inactive by Bernstein's crushing can be made to beat again by clamping the aorta and thus raising the endocardiac pressure.[5] Chemical stimulation is also effective. Delphinin,[6] quinine,[7] muscarin with atropin,[8] atropin alone,[9] morphin and various other alkaloids, dilute mineral acids, dilute alkalies, bile, sodium chloride, alcohol, and other bodies,[10] when painted on the resting ventricle, call forth a longer or shorter series of beats. Stimulation with induction shocks gives a similar result.[11]

[1] Scherhey, 1880, p. 260.   [2] Cushny, 1893, p. 451.   [3] Gaskell, 1883, p. 54.
[4] Bernstein, 1871, p. 230; Foster and Dewsmith, 1876, p. 737; von Basch, 1879, p. 71; Scherhey, 1880, p. 259; Langendorff, 1895, p. 336; Kaiser, 1895, p. 464.
[5] Gaskell, 1880, p. 51; Aubert, 1881, p. 366; Ludwig and Luchsinger, 1881, p. 231; Dastre, 1882, p. 458; Biedermann, 1884, p. 24; Langendorff, 1884, p. 6.
[6] Bowditch, 1871, p. 169.   [7] Schtschepotjew, 1879, p. 56.   [8] v. Basch, 1879, p. 73.
[9] Löwit, 1881, p. 447.   [10] Langendorff, 1884, p. 21; 1895, p. 333; Kaiser, 1895, p. 6.
[11] Bowditch, 1871, p. 149; Kronecker, 1875, p. 178; 1879, p. 381; 1880, p. 285; v. Basch, 1879, p. 71; Ranvier, 1880, p. 46; Dastre, 1882, p. 433; Gaskell, 1883, p. 52.

Other muscles in which no nerve-cells have been discovered can contract rhythmically. Thus the bulbus aortæ of the frog beats regularly after its removal from the body, even the smallest pieces showing under the microscope rhythmical contractions. Engelmann, who observed this fact, declares that the entire bulbus is lacking in nerve-cells. This is contradicted by Dogiel; yet it seems hardly reasonable that these " smallest pieces " which Engelmann mentions were each provided with ganglion-cells. It is more probable that the contractions were the result of a constant artificial stimulus.[1] Curarized striated muscles placed in certain saline solutions may contract from time to time.[2] The hearts of many invertebrates in which ganglion-cells are apparently absent beat rhythmically.[3]

Much has been made of the fact that the ganglion-cells grow into the heart long after the cardiac rhythm is established,[4] showing that the embryonic heart muscle has rhythmic contractile powers. The adult heart muscle, it is alleged, retains certain embryonic peculiarities of structure, and as structure and function are correlated, should also retain the embryonic power of contraction without nerve-cells.[5]

It cannot be denied that these facts prove that the embryo heart muscle possesses rhythmic contractility, that the apical half of the heart of the adult frog and tortoise may be made to contract rhythmically, and that even fully striated muscle will under some conditions show more or less periodic contractions. They can, however, hardly be said to prove that the beat of the mammalian or even the batrachian adult heart is not dependent on discharges from the cardiac nerve-cells. Even the freedom of the apex from ganglion-cells, which is the very foundation of the doctrine of muscular origin, has recently been questioned.[6] This problem is still unsolved.

The Excitation-wave.—The change in form which constitutes what commonly is called the cardiac contraction is preceded by a change in electrical potential, supposed to be a manifestation of the unknown process by which the heart-muscle is excited to contract. Both the contraction and the electrical change sweep over the heart in the form of waves, and it has become the custom to speak of the electrical change as the excitation-wave. It should not be forgotten, however, that this usage rests merely on an assumption, for the real nature of the excitation is still a mystery. The contraction-wave begins normally at the great veins, travels rapidly through the auricle, and, after a distinct interval, spreads through the ventricle. The excitation-wave, which precedes and is the cause of the contraction, probably takes the same course,[7] and in fact it is possible to show that the change in electrical potential actually begins under normal conditions at the great veins and passes thence over the entire heart. But this sequence is not invariable. The ventricle under abnor-

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[1] Engelmann, 1882, p. 446; Dogiel, 1894, p. 225.   [2] Biedermann, 1880, p. 259.

[3] Concerning the cardiac apex in fishes, see Ludwig and Luchsinger, 1881, p. 247; Kazem-Beck and Dogiel, 1882, p. 259; McWilliam, 1885, p. 197; Mills, 1886, p. 91.

[4] Wagner, 1854, p. 227; Schenck, 1867, p. 111; His, Jr., 1893, p. 25; Pickering, 1893, p. 391.

[5] Gaskell, 1883, p. 77.   [6] Berkeley, 1894, p. 90.   [7] Compare Kaiser, 1895, p. 447.

mal conditions has been seen to contract before the auricle, the normal sequence of great veins, auricle, and ventricle being reversed.[1]   The energy of the ventricular muscle-cell may, therefore, be discharged by an excitation arising within the ventricle itself.   Evidence of this is afforded also by the experiment of Wooldridge,[2] who isolated the ventricles by drawing a silk ligature tightly about the auricles at their junction with the ventricles, completely crushing the muscle and nerves of the auricle in the track of the ligature without tearing through the more resistant pericardium.   This experiment was repeated the following year by Tigerstedt,[3] who devised a special clamp for crushing the auricular tissues.   Both observers found that the auricles and ventricles continued to beat.   The rhythm, however, was no longer the same.   The ventricular beat was slower than before[4] and was independent of the beat of the auricle.   Thus the ventricle, no longer connected physiologically with the auricle, develops a rhythm of its own, an idio-ventricular rhythm.   It seems improbable that the very small part of the auricular tissue which cannot be included in Wooldridge's ligature for fear of closing the coronary arteries should be able to maintain the ventricular contractions.

Independent contraction is said to be secured by properly regulated excitation of the cardiac end of the cut vagus nerve.   Stimuli of one second duration applied to the vagus at intervals of six to seven seconds arrest the auricles completely, but do not stop the ventricles, except during the second of stimulation.   The ventricles, now dissociated from the auricles, beat with a rhythm different from that which characterized the normal heart.[5]   The force of this demonstration is somewhat weakened by the possibility that the auricles, although not beating themselves, might still excite the ventricles to contraction.

Conduction of the Excitation.—If the points of non-polarizable electrodes are placed on the surface of the ventricle and connected with a delicate galvanometer, a variation of the galvanometer needle will be seen with each ventricular beat.   If one electrode is placed near the base of the heart and the other near the apex it is seen that the former electrode becomes negative before the latter, indicating that the part of the heart muscle on which the basal electrode rests is stimulated before the apical portion, and that the difference in electrical potential, or excitation-wave, according to the prevailing hypothesis, travels as a wave over the ventricle from the base to the apex (see Fig. 112).   Burdon-Sanderson and Page[6] have found that the duration of the difference of potential is about two seconds in the frog's heart at ordinary temperatures.   Cooling lengthens the period of negativity, warming diminishes it.   Some observers

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[1] Recently studied by Engelmann, 1895, p. 275; see also Knoll, 1894, p. 306, who observed fibrillary contraction of the auricle coincident with strong co-ordinated contractions of the ventricles.

[2] Wooldridge, 1883, p. 527.

[3] Tigerstedt, 1884, p. 500; see also Krehl and Romberg, 1892, p. 54.

[4] The isolated ventricle may, however, beat as rapidly as the auricle, although independently of it (Bayliss and Starling, 1892, p. 408).

[5] Roy and Adami, 1892, p. 236; see also Knoll, 1884, p. 312.

[6] Burdon-Sanderson and Page, 1884, p. 338.

believe that the excitation-wave under certain conditions returns toward the base after having reached the apex.[1] The speed of the excitation-wave has been measured by the interval between the appearance of negative variation in the ventricle when the auricle is stimulated first near and then as far as possible
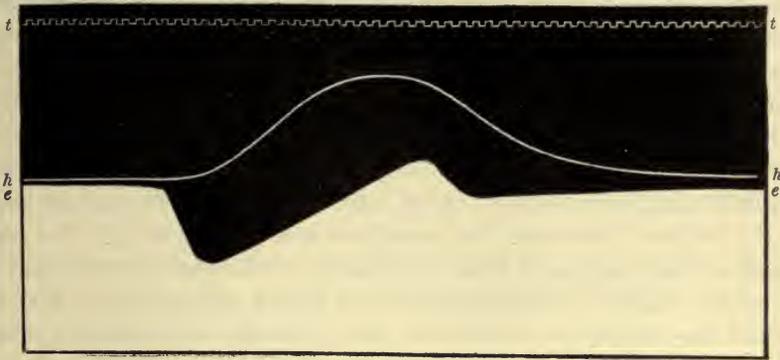
FIG. 112.—The electrical variation in the spontaneously contracting heart of the frog, recorded by a capillary electrometer, the apex being connected with the sulphuric acid and the base with the mercury of the electrometer. The changes in electrical potential are shown by the line *e, e,* which is obtained by throwing the shadow of the mercury in the capillary on a travelling sheet of sensitized paper. The contraction of the heart is recorded by the line *h, h*; time, in $\frac{1}{50}$ second, by *t, t.* The curves read from left to right. The electrical variation is diphasic; in the first phase the base is negative to the apex; in the second, the apex is negative to the base; the negative variation passes as a wave from base to apex (Waller, 1887, p. 231).

from the non-polarizable electrodes. The interval is the time which the excitation-wave requires to pass the distance between the two points stimulated. The average rate is at least 50 millimeters per second.[2] The negative variation begins apparently instantly after the application of the stimulus. Its phases and their characteristics have been described by Engelmann.[3]

The latent period of a frog's heart muscle is about 0.08 second.[4]

Although the normal course of the excitation-wave is from base to apex, it can be made to travel in any direction. If the frog's ventricle is cut with fine scissors into a number of pieces in such a way as to leave small bridges of heart-tissue between each piece, and any one of the pieces is stimulated, the contraction will begin in the stimulated piece and then run from piece to piece over the connecting bridges until all have successively contracted. The direction in which the excitation-wave travels can thus be altered at the pleasure of the operator.[5]

Whether the excitation is propagated from muscle-cell to muscle-cell or by means of nerve-fibres has given rise to much discussion. Anatomical evidence can be adduced on both sides. On the one hand the rich plexus of nerve-fibres everywhere present in the heart-muscle suggests conduction through nerves; on the other is the intimate contact of neighboring muscle-cells over

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[1] Bayliss and Starling, 1892, pp. 260, 380.

[2] Engelmann, 1878, p. 91; Burdon-Sanderson and Page, 1880, p. 426, give 150 millimeters per second.

[3] Engelmann, 1878, p. 74.   [4] *Ibid.,* 1874, p. 6.

[5] *Ibid.,* p. 3; compare Bayliss and Starling, 1892, p. 262.

a part at least of their surface, thus bringing one mass of irritable protoplasm against another and offering a path by which the excitation might travel from cell to cell.[1]

If the excitation-wave were conducted by means of nerves, the difference between the moment of contraction of the ventricle when the auricle is stimulated near the ventricle, and again as far as possible from the ventricle, should be very slight, because of the great speed at which the nervous impulse travels (about 33 meters per second). If, on the contrary, the conduction were by means of muscle, the difference would be relatively much greater, corresponding to the much slower conductivity of muscular tissue. It has been found by Engelmann that the ventricle contracts later when the auricle is stimulated far from the ventricle than when it is stimulated near the ventricle. The rate of propagation being calculated from the difference in the time of ventricular contraction was found to be 90 millimeters per second, which is about 300 times less than the rate which would have been obtained had conduction over the measured distance taken place through nerves.[2] Hence the stimulus that travels through the auricle to the ventricle and causes its contraction should be propagated in the auricle by muscle-fibres and not by nerves.

Passage of Excitation-wave from Auricle to Ventricle.—The normal contraction of the heart begins, as has been said, at the junction of the great veins and the auricle, spreads rapidly over the auricle and, after a distinct pause, reaches the ventricle. The normal excitation-wave preceding the contraction passes likewise from the auricle to the ventricle and is delayed at or near the auriculo-ventricular junction. The controversy over the nervous or muscular conduction of the excitation within the auricle and ventricle has been extended to its passage from auricle to ventricle. A path for conduction by nerves is presented by the numerous nerves which go from the auricle to the ventricle. It has been shown recently that muscular connections also exist.[3] In the frog, muscle-bundles pass from the auricle to the ventricle where the auricular septum adjoins the base of the ventricle. Muscular bridges pass also from the sinus venosus to the auricles and from the ventricle to the bulbus arteriosus.[4] These muscle-fibres appear to be in intimate contact with the muscle-cells of the divisions of the heart which they unite. Gaskell[5] believes that the connecting fibres are morphologically and physiologically related to embryonic muscle, and therefore possess the power of contracting rhythmically.

The delay experienced by the excitation in its passage from the auricle to the ventricle—in other words, the normal interval between the contraction of the auricle and the contraction of the ventricle—is explained by those favoring

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[1] Engelmann, 1874, p. 7.

[2] *Ibid.*, 1894, p. 188; 1896, p. 549; the measurements of Bayliss and Starling, 1892, p. 271, on the mammalian heart are probably of little value because of the variation due to temperature (p. 272). See also Kaiser, 1895, p. 2, and Engelmann's reply, 1896, p. 547.

[3] Paladino, 1876; Gaskell, 1880, p. 70; Krehl and Romberg, 1892, p. 71; Kent, 1893, p. 240; Engelmann, 1894, p. 158.

[4] Engelmann, 1894, p. 158.   [5] Gaskell, 1883, p. 77.

the nervous conduction as the delay which the excitation experiences in discharging the ganglion-cells of the ventricle, in accordance with the well-known hypotheses of the retardation of the nerve-impulse in sympathetic ganglia and the slow passage of the nervous impulse through spinal cells.

The explanation given by those who believe in muscular conduction is that the small number of muscular fibres composing the bridge between auricle and ventricle acts as a " block " to the excitation-wave. If the auricle of the tortoise heart is cut into two pieces connected by a small bridge of auricular tissue, the stimulation of one piece will be followed immediately by the contraction of that piece, and after an interval by the contraction of the other. The smaller the bridge, the longer the interval; that is the longer the excitation-wave will be in passing from one piece to another.[1]

·The duration of the pause or " block " in the frog has been found to be from 0.15 to 0.30 second. The length of the muscle-fibres connecting auricle and ventricle is about one millimeter. The speed of the excitation-wave in embryonic heart muscle is from 3.6 to 11.5 millimeters per second. The duration of the pause agrees, therefore, with the time which would be required for muscular conduction.[2]

The extensive extirpations of the auricular nerves which have been made without stopping conduction from auricle to ventricle[3]—for example, the extirpation of the entire auricular septum of the frog's heart—are of little importance to this question, since the great number of nerve-cells revealed by recent methods make it improbable that any extirpation short of total removal of both auricles could cut off all the nerve-cells of the auricle.

Refractory Period and Compensatory Pause.—Schiff[4] found in 1850 that the heart which contracted to each stimulus of a series of slowly repeated mechanical stimuli would not contract to the same stimuli if they followed each other in too rapid succession. Kronecker[5] got a similar result with induction shocks. The heart contracted to every stimulus only when the interval between them was not too brief. The following year Marey[6] published a systematic study of the phenomenon. He observed that the irritability of the heart sank during a part of the systole, but returned during the remainder of the systole and the following diastole.[7] The stimulus which fell between the beginning of the systole and its maximum produced no extra contraction, whilst that which fell between the maximum of one systole and the beginning of the next called forth an extra contraction. During a part of the cardiac cycle therefore the heart is " refractory " toward stimuli. The irritability of the heart is removed for a time by an adequate stimulus.

Kronecker and Marey noticed further that stimulation with the induction shock during the non-refractory period did not influence the total number of systoles. The extra systole called forth by the artificial stimulus was followed by a pause the length of which was that of the normal pause plus the interval

[1] Gaskell, 1883, p. 64.
[2] Engelmann, 1894, p. 159.
[3] Gaskell, 1883, p. 75; Hoffmann, 1895, p. 169.
[4] Schiff, 1850, p. 50.
[5] Kronecker, 1875, p. 181.
[6] Marey, 1876, p. 73.
[7] Cf. Engelmann, 1895, p. 313.

between the appearance of the extra systole and what would have been the end of the cardiac cycle in which the extra systole fell. The extra length of this pause restored the normal frequency or rhythm. It was called the compensatory pause (see Fig. 113).
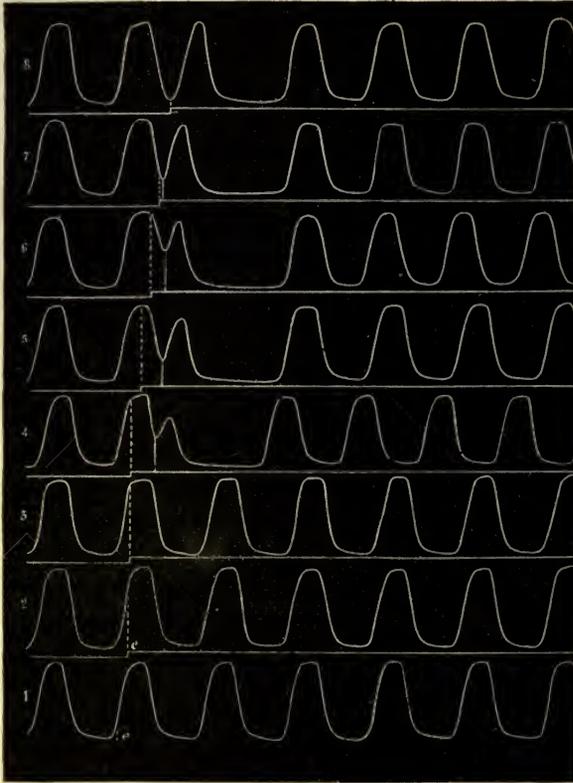
FIG. 113.—The refractory period and compensatory pause. The curves are recorded by a writing lever resting on the ventricle of the frog's heart. They read from left to right. A break in the horizontal line below each curve indicates the moment at which an induction shock was sent through the ventricle. In curves 1, 2, and 3 the ventricle proved refractory to this stimulus; in the remaining curves, the stimulus having fallen outside the refractory period, an extra contraction and compensatory pause are seen. Many of the phenomena mentioned in the text are illustrated by this figure (Marey, 1876, p. 72).

If the heart, or the isolated apex, is beating at a rate so slow that an extra contraction falling in the interval between two normal contractions has time to complete its entire phase before the next normal contraction is due, there will be no compensatory pause.[1]

The refractory phase disappears with sufficiently strong stimuli, especially if the heart is warmed.[2] In such a case an artificial stimulus falling in the beginning of a spontaneous contraction produces an extra contraction. This extra contraction, however, comes first after the end of the systole during which the artificial stimulation is made,[3] occurring in fact toward the end of the

[1] Kaiser, 1895, p. 449.

[2] Engelmann, 1882, p. 453; compare Burdon-Sanderson and Page, 1880, p. 401.

[3] This is apparently true only of the whole heart, and not of the isolated apex (Engelmann, 1895, p. 317).

following diastole. The latent period of such a contraction lengthens with the length of the interval between the artificial stimulation and the end of the systole.

A refractory period has been demonstrated in the auricle of the frog[1] and dog ;[2] in the ventricle of the cat,[3] rabbit and dog,[4] and in the sinus venosus[5] and bulbus arteriosus[6] of the frog.

In some cases, the extra stimulus provokes not merely one, but two or three extra contractions.[7]

The amplitude of the extra contraction increases with the length of the interval between the maximum of contraction and the extra stimulus. If the extra stimulus is given at the beginning of relaxation, the extra contraction is exceedingly small ; on the other hand, the extra contraction may be greater than the primary one, when the stimulus falls in the pause between two normal beats.[8]

The supplementary systole of the auricle is sometimes followed by a supplementary systole and compensatory pause of the ventricle, sometimes by the compensatory pause alone, probably because the excitation wave reaches the ventricle during its refractory period.[9] Multiple extra contractions of the auricle are often followed by the same number of extra contractions of the ventricle.[10] If the frog's heart is made to beat in reversed order, ventricle first, auricle second, extra contractions of the ventricle may be produced, and will cause extra contractions of the auricle with compensatory pause. If the reversed excitation wave travelling from the ventricle to the auricle reaches the latter during auricular systole, the extra auricular contraction is omitted, but a distinct though shortened compensatory pause is still observed. The phenomena with reversed contraction are therefore similar to those seen under the usual conditions.[11]

Kaiser[12] finds in frogs poisoned with muscarin that stimulation of the ventricle during the refractory period causes the contraction in which the stimulus falls to be more complete, as shown by the contraction curve rising above its former level. He concludes that the ventricle is not wholly inexcitable even during the refractory period.

The question whether the refractory state and compensatory pause are properties of the muscle-substance or of the nervous system of the heart has excited considerable attention. If the ganglion-free apex of the frog's ventricle is stimulated by rapidly repeated induction shocks it can be made to contract periodically for a time. By momentarily increasing the strength of any one induction shock an extra stimulus can be given from time to time. When

[1] Hildebrand, 1877, quoted by Lovén, 1886, p. 5 ; Brunton and Cash, 1883, p. 461 ; Kaiser, 1895, p. 15 ; Engelmann, 1895, p. 322.   [2] Meyer, 1893, p. 185.

[3] McWilliam, 1888, p. 169.   [4] Gley, 1889, p. 501 ; 1890, p. 437.

[5] Strömberg and Tigerstedt, 1888, p. 26 ; Brunton and Cash, 1883, p. 463.

[6] Engelmann, 1882, p. 453.

[7] Hildebrand, 1877 ; Strömberg and Tigerstedt, 1888, p. 33 ; Meyer, 1893, p. 187.

[8] Strömberg and Tigerstedt, 1888, p. 36.   [9] Kaiser, 1895, p. 16.

[10] Meyer, 1893, p. 188.   [11] Kaiser, 1895, p. 19.   [12] *Ibid.*, 1892, p. 219.

the extra stimulus falls after the contraction maximum or during diastole an extra contraction results, otherwise not. The refractory period exists, therefore, independently of the cardiac ganglia.[1]

The compensatory pause can also, though not always, be secured with the ganglion-free apex.[2]

The refractory period has been used to show how a continuous stimulus might produce a rhythmic heart-beat. The continuous stimulus cannot affect the heart during the refractory period from the beginning to near the maximum of systole. At the close of the refractory period the constant stimulus becomes effective, causing an extra contraction with long latent period. This latent period is, according to this theory, the interval between the first and the second contraction.[3]

A tonic contraction of the heart muscle is sometimes produced by strong, rapidly repeated induction shocks[4] and by various other means, such as filling the ventricle with old blood,[5] by weak sodium hydrate solution,[6] and by certain poisons, such as digitalin and veratrin.[7]

A. The Cardiac Nerves.

The cardiac nerves are branches of the vagus and the sympathetic nerves.

In the *dog* the vagus arises by about a dozen fine roots from the ventrolateral aspect of the medulla and passes outward to the jugular foramen in company with the spinal accessory nerve. In the jugular canal the vagus bears a ganglion called the jugular ganglion. The spinal accessory nerve joins the vagus here, the spinal portion almost immediately leaving the vagus to be distributed to certain muscles in the neck, while the medullary portion passes to the heart through the trunk ganglion and thereafter in the substance of the vagus. Directly after emerging from the skull, the vagus presents a second ganglion, fusiform in shape and in a fairly large dog about one centimeter in length. From the caudal end or middle of this " ganglion of the trunk " is given off the superior laryngeal nerve, slightly behind which a large nerve is seen passing from the sympathetic chain to the trunk of the vagus. This nerve is in reality the main cord of the sympathetic chain, the sympathetic nerve being bound up with the vagus from the " inferior " cervical ganglion to the point just mentioned. Posterior to the trunk ganglion of the vagus, the vago-sympathetic runs caudalward as a large nerve dorsal to the common carotid artery as far as the first rib or near it, where it enters the so-called inferior cervical ganglion. This ganglion belongs to the sympathetic system and not to the vagus; from a morphological point of view it is the middle cervical sympathetic ganglion. The true inferior cervical sympathetic

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[1] Dastre, 1882, p. 447; Kaiser, 1895, p. 449; Engelmann, 1895, p. 326; compare Kronecker, 1875, p. 181.

[2] Kaiser, 1895, pp. 449, 457; Engelmann, 1895, p. 311; Dastre dissents, 1882, p. 464.

[3] Tigerstedt, 1893, p. 169.   [4] Engelmann, 1882, p. 453.

[5] Aubert, 1881, p. 381; compare Rossbach, 1874, p. 97.

[6] Gaskell, 1880, p. 53.   [7] Roy, 1879, p. 477.

ganglion is fused with the first one or two thoracic ganglia to form the ganglion stellatum, situated opposite the first intercostal space. At the " inferior cervical " ganglion the vagus and the sympathetic part company, the vagus passing caudalward behind the root of the lung and the sympathetic passing to the stellate ganglion, dividing on its way into two portions (the annulus of Vieussens), which embrace the subclavian artery. In many cases the lower loop of the annulus of Vieussens joins the trunk of the vagus caudal to the ganglion.[1]

The cardiac nerves spring from the vagus and the sympathetic nerve in the region of the inferior cervical ganglion. They may be divided into an inner and an outer group.

The inner group is composed of one medium, one thick, and from two to three slender nerves. The nerve of medium thickness springs from the ganglion itself. The thick branch rises from the trunk of the vagus near the origin of the inferior laryngeal nerve about 1.25 centimeters caudal to the inferior cervical ganglion. It can be easily followed to its final distribution. It passes behind the vena cava superior, perforates the pericardium, and runs parallel with the ascending aorta across the pulmonary artery, on which it lies in the connective tissue already divided into two or three tolerably thick twigs or spread in a fan of smaller branches. These now bend beneath the artery, pass round its base on the inner side, and reach the anterior inter-ventricular groove. Here they spread over the surface of the ventricle. The slender branches leave the vagus trunk caudal to the branch just described.

The outer group comprises two thick branches—namely, an upper nerve, springing from the ganglion or from the trunk of the vagus near it, and a lower nerve, from the lower loop of the annulus, or from the vagus 1–1½ centimeters lower down. Each of these thick branches may be replaced by a bundle of finer branches, and in fact the description of the cardiac nerves

FIG. 114.—Cardiac plexus and stellate ganglion of the cat, drawn from nature after the removal of the arteries and veins; about one and one-half times natural size (Boehm, 1875, p. 258):

R, right; *L*, left: 1, 1, vagus nerve; 2, cervical sympathetic; 2′, annulus of Vieussens; 2″, thoracic sympathetic; 3, recurrent laryngeal nerve; 4, depressor nerve, entering the vagus on the right, on the left running a separate course to the heart; 5, middle (often called "inferior") cervical ganglion; 5′, communicating branch between middle cervical ganglion and vagus nerve; 6, stellate ganglion; 6′, 6″ 6‴, spinal roots of stellate ganglion; 7, communication between stellate ganglion and vagus; 8′, 8″, 8‴, cardiac nerves.

here given can be regarded as a close approximation only, so frequent are the individual variations.[2]

[1] Schmiedeberg, 1871, p. 34.

[2] Details concerning the composition of the cardiac plexuses in the dog are given by Lim Boon Keng, 1893, p. 467.

In the *rabbit* the cervical sympathetic and the vagus trunk are not joined, as in the dog, but run a separate course. Cardiac fibres from the spinal cord reach the lower cervical and first thoracic ganglion (ganglion stellatum) along their rami communicantes [1] and pass to the heart by two sympathetic cardiac nerves, one from the inferior cervical ganglion and one from the ganglion stellatum.[2]

The arrangement of the cardiac nerves in the *cat* is shown in Figure 114.

In the *frog* the cardiac nerves, both vagal and sympathetic, reach the heart through the splanchnic branch of the vagus. The sympathetic fibres pass out of the spinal cord with the third spinal nerve, through the ramus communicans of this nerve into the third sympathetic ganglion,[3] up the sympathetic chain to the ganglion of the vagus, and down the vagus trunk to the heart.[4]

The Inhibitory Nerves.

In 1845, Ernst Heinrich and Eduard Weber [5] announced that stimulation of the vagus nerves or the parts of the brain where they arise slows the heart even to arrest. When one pole of an induction apparatus was placed in the nasal cavity of a frog and the other on the spinal cord at the fourth or fifth vertebra, the heart was completely arrested after one or two pulsations and remained motionless several seconds after the interruption of the current. During the arrest, the heart was relaxed and filled gradually with blood. When the stimulus was continued many seconds, the heart began to beat again, at first weakly and with long intervals, then more strongly and frequently, until at length the beats were as vigorous and as frequent as before, though all this time the stimulation was uninterrupted.

In order to determine from what part of the brain this influence proceeds, the electrodes were brought very near together and placed upon the cerebral hemispheres. The movements of the heart were not affected. Negative results followed also the stimulation of the spinal cord. Not until the medulla oblongata between the corpora quadrigemina and the lower end of the calamus scriptorius was stimulated did the arrest take place. Cutting away the spinal cord and the remainder of the brain did not alter the result.

Having determined that the inhibitory power had its seat in the medulla oblongata, the question arose through what nerve the inhibitory influence is transmitted to the heart. In a frog in which the stimulation of the medulla had stopped the heart, the vagus nerves were cut and the ends in connection with the heart stimulated. The heart was arrested as before.

Thus the fundamental fact of the inhibition of a peripheral motor mechanism by the central nervous system through the agency of special inhibitory

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[1] Bever and von Bezold, 1867, pp. 236, 247.

[2] Ludwig and Thiry, 1864, p. 429; Bever, 1867, p. 249.

[3] It is probable that the fibres of spinal origin end in the sympathetic ganglia, making contacts there with sympathetic ganglion-cells, the axis-cylinder processes of which pass up the cervical chain and descend to the heart in company with the vagus.

[4] Gaskell and Gadow, 1884, p. 369.   [5] E. Weber, 1846, p. 42.

nerves was firmly established. A great number of investigations have demonstrated that this inhibitory power is found in many if not all vertebrates and not a few invertebrates.[1]

The effect of vagus stimulation on the heart is not immediate; a *latent period* is seen extending over one beat and sometimes two, according to the moment of stimulation[2] (see Fig. 115).
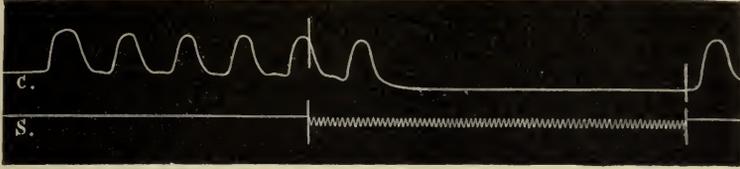
FIG. 115.—Pulsations of frog's heart, inhibited by the excitation of the left vagus nerve (Tarchanoff, 1876, p. 296): *C*, pulsations of heart; *S*, electric signal which vibrated during the passage of the stimulating current, one vibration for each induction shock.

Changes in the Ventricle.—The *periodicity* of the ventricular contraction is altered by vagus excitation, a weak excitation lengthening the duration of diastole, while leaving the duration of systole unchanged (see Fig. 116). A stronger excitation, capably of modifying largely the force of the contraction, lengthens both systole and diastole.[3] The difficulty of producing a continued arrest in diastole is much greater in some animals than in others. Even when easily produced, the arrest soon gives away in the manner described by E. H. and E. Weber, the heart beginning to beat in spite of the vagus excitation.[4]
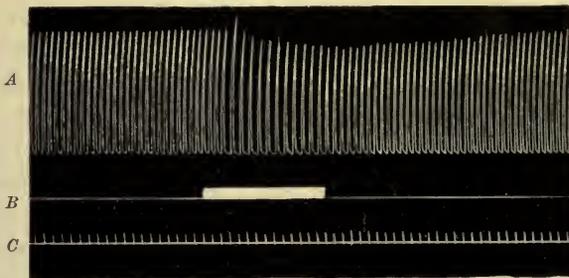
FIG. 116.—Showing the lengthened diastole and diminished force of ventricular contraction during weak stimulation of the peripheral end of the cut vagus nerve. The heart (cat) was isolated from both systemic and pulmonary vessels, and was kept beating by circulating defibrinated blood through the coronary arteries: *A*, Pressure in left ventricle, which was filled with normal saline solution, and communicated with a Hürthle membrane manometer by means of a cannula which was passed through the auricular appendix and the mitral orifice; *B*, line drawn by the armature of an electro-magnet in the primary circuit; the heavy line indicates the duration of stimulation; *C*, time in seconds.

The *force of the contraction*, measured by the height of the up-stroke of the intra-ventricular pressure curve, or by placing a recording lever on the heart,

[1] For literature see Tigerstedt, *Physiologie des Kreislaufes*, 1893.

[2] Schiff, 1849, p. 192; Pflüger, 1865, p. 30; Czermak, 1868, p. 644; 1868, p. 32; Donders, 1868, p. 339; 1872, p. 6; Tarchanoff, 1876, p. 300; Pruszynski, 1889, p. 569.

[3] Arloing, 1894, p. 88; Meyer, 1894, p. 698.

[4] Hough, 1895, p. 161. The terrapin heart is said not to escape, as a rule, from vagus inhibition. Compare Mills, 1885, p. 255; see also Laulanié, 1889, p. 409.

is lessened,[1] this diminution in force appearing often before any noticeable change in periodicity.

The *diastolic pressure* increases, as is shown by the lower level of the curve gradually rising farther and farther above the atmospheric pressure line.[2]

The *volume of blood* in the ventricle at the close of diastole is increased. So also is the volume at the close of systole (residual blood)—sometimes to such a degree that the volume of the heart at the end of systole may be greater than the volume of the organ at the end of diastole before the vagus was excited.[3]

The *output and the input* of the ventricle, that is, the quantity of blood discharged and received, are both diminished by vagus excitation.[4]

The *ventricular tonus,* or state of constant slight contraction on which the systolic contractions are superimposed, is also diminished, as is well shown by an experiment of Stefani.[5] In this experiment the pericardial sac is filled with normal saline solution under a pressure just sufficient to prevent the expansion of the heart in diastole. On stimulation of the vagus, the heart dilates further. A considerably higher pressure is necessary to overcome this dilatation. Stefani finds also that the pressure necessary to prevent diastolic expansion is much greater with intact than with cut vagi. Furthermore, the heart is much more easily distended by the rise of arterial pressure through compression of the aorta when the vagi are severed than when they are intact. Franck has noticed that the walls of the empty ventricle become softer when the vagus is stimulated.[6]

The *propagation of the cardiac excitation* is more difficult during vagus excitation.[7] Bayliss and Starling[8] demonstrate this on mammalian hearts made to contract by exciting the auricle three or four times per second ; the ventricle as a rule responds regularly to every auricular beat. If, then, the vagus is stimulated with a weak induced current, the ventricle may drop every other beat, or may for a short time cease to respond at all to the auricular contractions. The defective propagation is not due to changes in the auricular contraction, for even an almost inappreciable beat of the auricle can cause the ventricle to contract. Nor is it due to lowered excitability of the ventricle, for the effect described is seen with currents too weak to depress the irritability of the ventricle to an appreciable extent.

The action of the vagus is accompanied by an *electrical variation.* This has been shown in the muscular tissue of the resting auricle of the tortoise[9] (see Fig. 117). The auricle is cut away from the sinus without injuring the coronary nerve, which in the tortoise passes from the sinus to the auricle and contains the cardiac fibres of the vagus. After this operation the auricle and ventricle remain motionless for a time, and this quiescent period is utilized for

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[1] Coats, 1869, p. 187 ; Nuël, 1874, p. 87 ; Gaskell, 1882, p. 1011 ; Heidenhain, 1882, p. 388 ; Mills, 1885, p. 283. Roy and Adami, 1892, p. 224, are of contrary opinion.

[2] Roy and Adami, 1892, p. 227.

[3] Roy and Adami, 1892, p. 218 ; compare Stefani, 1893, p. 136 ; 1895, p. 175.

[4] Roy and Adami, 1892, pp. 217, 228.   [5] Stefani, 1891, p. 182.

[6] Franck, 1891, p. 486.   [7] Gaskell, 1883, p. 100 ; McWilliam, 1888, p. 367.

[8] Bayliss and Starling, 1892, p. 412.   [9] Gaskell, 1887, p. 116 ; 1887, p. 404.

the experiment. The tip of the auricle is injured by immersion in hot water, and the demarcation current (the injured tissue being negative toward the uninjured) is led off to a galvanometer. On exciting the vagus in the neck, the demarcation current is markedly increased. No visible change of form is seen in the auricular strip.
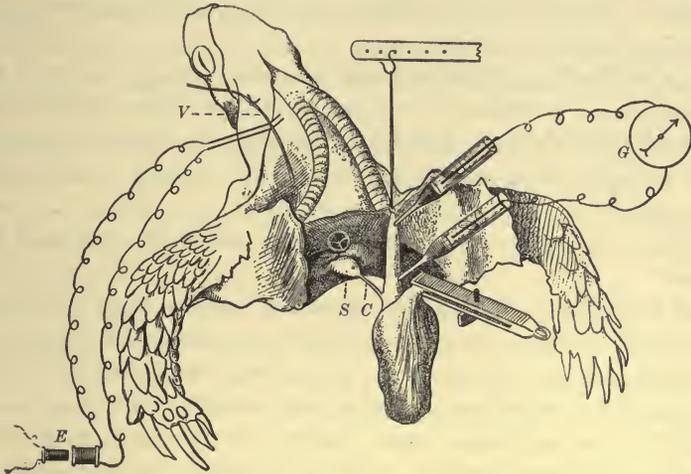
Fig. 117.—The tortoise heart prepared for the demonstration of the electrical change in the cardiac muscle accompanying the excitation of the vagus nerve: *V*, vagus nerve; *C*, coronary nerve; *S*, sinus and part of auricle in connection with it; *G*, galvanometer, in the circuit formed by two non-polarizable electrodes and the part of the auricle between them; *E*, induction coil (Gaskell, 1887).

Changes in the Auricle.—There is little probability that the action of the vagus on the auricle[1] differs essentially from the action on the ventricle. The force of the auricular contraction is diminished. The diastole is lengthened. The change in force appears earlier than in the change in periodicity, and sometimes without it. On the whole, the auricle is more easily affected by vagus excitation than the ventricle.

Action on Bulbus Arteriosus.—If the bulbus arteriosus of the frog's heart is extirpated in such a way as to leave untouched the nerve-fibres that connect it with the auricular septum, the contractions of the isolated bulbus will be arrested when the peripheral end of the vagus is excited.[2]

Diminished Irritability of Heart.—During vagus excitation with currents of moderate strength, the arrested heart will respond to direct stimulation by a single contraction. With strong vagus excitation, however, the directly stimulated heart contracts not at all or less readily than before.[3]

Effects of Varying the Stimulus.—A single excitation of the vagus does not stop the heart.[4] Morat has investigated the effect of excitations of varied

[1] Eckhard, 1860, p. 140; Nuël, 1874, p. 86; Gaskell, 1882, p. 1010; 1883, p. 89; Mills, 1885, p. 250; 1886, p. 550; McWilliam, 1885, p. 225; 1887, p. 309; 1888, p. 348; Johansson and Tigerstedt, 1889; Franck, 1891, p. 581; Bayliss and Starling, 1892, p. 410; Roy and Adami, 1892, p. 219. [2] Dogiel, 1894, p. 227.

[3] Schiff, 1850, p. 64; 1877, p. 494; Einbrodt, 1859, p. 353; Eckhard, 1883, p. 25; McWilliam, 1885, p. 222; 1888, p. 351; Mills, 1888, p. 3.

[4] Donders, 1868, p. 344; 1872, p. 5; Tarchanoff, 1876, p. 303; Heidenhain, 1882, p. 386.

duration, number, and frequency on the tortoise heart.[1]   With excitations of the same duration, the effect was minimal at 2 per second, maximal at 7 per second, diminishing thereafter as the frequency increased.   The longer the stimulation, the longer (within limits) was the inhibition.   An excitation that is too feeble or too slow, or, on the contrary, is over-strong or over-frequent, has no effect.   Within limits, however, the degree of inhibition increases with the strength of the stimulus.[2]

Weak stimuli affect primarily the auricles, diminishing frequency and force of contraction, and secondarily lower the frequency of the ventricle.   Stronger stimuli arrest the auricle, the ventricles continuing to beat with almost undiminished force but with altered rhythm.   Still stronger stimuli inhibit the ventricles also.[3]

The frequency can be kept comparatively small by continued moderate stimulation.[4]

Arrest in Systole.—The excitation of the tortoise vagus in the upper or middle cervical region is sometimes followed, according to Rouget,[5] by a state of continued, prolonged contraction—in short, an arrest in systole.   The same effect is observed in rabbits strongly curarized and in curarized frogs.   Arloing[6] noticed that the mechanical irritation produced by raising on a thread the left vagus nerve of a horse caused the right ventricle to remain contracted during seven seconds.   The ventricular curve during this time presented the characters of the tetanus curve of a striated muscle.[7]

Comparative Inhibitory Power.—One vagus often possesses more inhibitory power than the other.[8]

Septal Nerves in Frog.—The electrical stimulation of the peripheral stump of either of two large nerves of the inter-auricular septum in the frog alters the tonus and the force of contraction of the ventricle, but not the frequency.   After section of these nerves, the excitation of the vagus has very little effect on the tonus, and almost none on the force of the ventricular beat, while the frequency is diminished in the characteristic manner.   Evidently, therefore, the two large septal nerves take no part in the regulation of frequency, but leave this to the nerves diffusely distributed through the auricles.   There is then an anatomical division of the septal branches of the frog's vagus, the fibres affecting periodicity running outside the septal nerves, while those modifying the force of contraction and the tonus of the ventricle run within them.[9]

[1] Morat, 1894, p. 10; Legros and Onimus, 1872, p. 565.

[2] v. Bezold, 1863, p. 50; Pflüger, 1859, p. 19; Donders, 1868, p. 356.

[3] Johansson and Tigerstedt, 1889; Roy and Adami, 1892, p. 237; Bayliss and Starling, 1892, p. 411.   [4] Laulanié, 1889, p. 408.

[5] Rouget, 1894, p. 398.   [6] Arloing, 1893, p. 112.

[7] For other unusual alterations in the heart-beat in consequence of vagus excitation see Arloing, 1893, p. 163.

[8] *Cold-blooded Animals:* Meyer, 1869, p. 61; Tarchanoff, 1876, p. 293; Gaskell, 1882, p. 82; McWilliam, 1885, xvi.; Mills, 1885, p. 259; 1887, p. 11; 1888, p. 2.

Mammals: Masoin, 1872, p. 410; Legros and Onimus, 1872, p. 575; Arloing and Tripier, 1872, p. 420; Langendorff, 1878, p. 68; compare Brown-Séquard, 1880, p. 211.

[9] Hofmann, 1895, p. 169; examine Eckhard, 1876, p. 192; and Dogiel, 1890, p. 258.

Nature of Vagus Influence on Heart.—The nature of the terminal apparatus by which the vagus inhibits the heart is unknown. It is probable that the same intracardiac apparatus serves for both nerves, for Hüfler finds that when the heart escapes from the inhibition caused by continued stimulation of one vagus, the prolonged diastole growing shorter again, the immediate stimulation of the second vagus has no effect upon the heart.[1] Dogiel and Grahe have recently observed that the lengthening of diastole which follows stimulation of the peripheral stump of the vagus, the other vagus being intact, is less marked than when both vagi are cut.[2]

The question whether the vagus acts on the heart muscle directly or through the medium of some nervous mechanism has not yet been answered. The only fact bearing immediately on this problem is the diminution in the irritability of the ventricle during vagus excitation, and this does not exclude an action upon a nervous mechanism.[3]

The earlier attempts to form a satisfactory theory for the inhibitory power of the vagus met with little success. The statement of the Webers' that the vagus inhibits the movements of the heart gave to nerves a new attribute, but is hardly an explanation. The view of Budge[4] and Schiff,[5] that the vagus is the motor nerve of the heart and that inhibition is the expression of its exhaustion, is now of only historical interest. Nor has a better fate overtaken the theory of Brown-Séquard,[6] who saw in the vagus the vaso-motor nerve of the heart, the stimulation of which, by narrowing the coronary arteries, deprived the heart of the blood that, according to Brown-Séquard, is the exciting cause of the contraction.

Of recent years, the explanation that has commanded most attention is the one advanced by Stefani[7] and Gaskell, namely, that the vagus is the trophic nerve of the heart, producing a dis-assimilation or katabolism in systole and an assimilation or anabolism in diastole. Gaskell supports this theory by the observation that the after-effect of vagus excitation is to strengthen the force of the cardiac contraction and to increase the speed with which the excitation wave passes over the heart, while the contrary effects are witnessed after the excitation of the augmentor nerves.[8]

Various attempts have been made to prove a trophic action of the vagus on the heart by cutting the nerve in animals kept alive until degenerative changes

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[1] Hüfler, 1889, p. 307; Hough, 1895, p. 198. Earlier experimenters obtained conflicting results; see Tarchanoff and Puelma, 1875, p. 757; Tarchanoff, 1876, p. 296; Eckhard, 1879, p. 181; Gamgee and Priestley, 1878, p. 39; Tscherepin, 1881; McWilliam, 1885, p. 217; Mills, 1885, p. 257; Laulanié, 1889, p. 377.

[2] Dogiel and Grahe, 1895, p. 393.

[3] Changes in the peripheral efficiency of the vagi are discussed by McWilliam, 1893, p. 475.

[4] Budge, 1846, p. 418.   [5] Schiff, 1849, p. 442.

[6] Brown-Séquard, 1853, p. 154.

[7] Stefani, 1880; 1895, p. 176; Eichhorst, 1879, p. 18; Gaskell, 1886, p. 49; Fantino, 1888, p. 243; Timofeew, 1889; Tigerstedt, 1893, p. 259. Gaskell gives a résumé of his work on the heart in *Archives de Physiologie*, 1888, pp. 56–68.

[8] Gaskell, 1883, pp. 81, 94; also Gianuzzi, 1871; Schiff, 1878, p. 16; Brown-Séquard, 1880, p. 211; Laffont, 1887, p. 1095; Konow and Stenbeck, 1889, p. 414.

in the heart-muscle should have had time to appear. The important distribution of the vagus nerve to many organs, and the consequently wide extent of the loss of function following its section, makes it difficult to decide whether the changes produced in the heart are not secondary to the alterations in other tissues. The work of Fantino[1] will serve for an example of these investigations. Fantino cut a single vagus to avoid the paralysis of deglutition and the inanition and occasional broncho-pneumonia that follow section of both nerves. Young and perfectly healthy rabbits and guinea-pigs were selected. The operation was strictly aseptic, and all cases in which the wound suppurated were excluded. A piece of the nerve about one centimeter long was cut out, so that no reunion could be possible. After the operation the animals were as a rule lively, ate well, and gained weight. Post-mortem examination of animals killed two days or more after section of the vagus nerve disclosed no pathological changes in the lungs, spleen, liver, and stomach. In the heart, areas were found in which the nuclei and the striation of the muscle-cells had disappeared. Eighteen days after section the atrophy of the cardiac muscle in these areas was observed to be extreme. The degenerations following section of the right vagus were situated in a different part of the ventricular wall from those following section of the left nerve.

The effects of stimulation of the *vagus nerve in the new-born* do not differ essentially from those seen in the adult.[2]

The relation between the action of the *vagus and the intracardiac pressure* has been recently studied by Stewart.[3] He finds that an increase in the pressure in the sinus or auricle makes it difficult to inhibit the heart through the vagus.

The inhibitory action of the vagus diminishes as the *temperature*[4] of the heart falls. At a low limit the inhibitory power is lost, but may return when the heart is warmed again. Even when the stimulation of the trunk of the nerve has failed to affect the cooled heart, the direct stimulation of the sinus can still cause distinct inhibition. The power of inhibiting the ventricle is first lost. Loss of inhibitory power does not follow the raising of the heart to high temperatures. The vagus remains active to the verge of heat rigor, and resumes its power as soon as the rigor passes away.

THE AUGMENTOR NERVES.

v. Bezold[5] observed in 1862 that stimulation of the cervical spinal cord caused an increased frequency of heart-beat. This seemed to him to prove the existence of special accelerating nerves. Ludwig and Thiry,[6] however, soon pointed out that stimulation of the spinal cord in the cervical region excited many vaso-constrictor fibres, leading to the narrowing of many vessels and a corresponding rise of blood-pressure. The acceleration of the heart-beat

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[1] Fantino, 1888, p. 239; see also Bidder, 1868, p. 41; Eichhorst, 1879, p. 18; Wassilieff, 1881, p. 317; Klug, 1881, p. 946.

[2] Compare Soltmann, 1877, p. 106; Bochefontaine, 1877, p. 226; Tarchanoff, 1878, p. 217; Langendorff, 1879, p. 247; von Anrep, 1880, p. 78; Meyer, 1893, p. 477.

[3] Stewart, 1892, p. 138.   [4] Stewart, 1892, p. 80.

[5] von Bezold, 1863, p. 191.   [6] Ludwig and Thiry, 1864, p. 421.

accompanying this rise in blood-pressure would alone explain the observation of von Bezold. Three years later Bever and von Bezold[1] were more successful. The influence of the vaso-motor nerves was excluded by section of the spinal cord between the first and second thoracic vertebræ. Stimulation of the cervical cord now caused an increase in the frequency of the heart-beat without a simultaneous increase of blood-pressure. The fibres carrying the accelerating impulse were traced from the spinal cord to the last cervical ganglion and from there toward the heart.

In the *dog* the "augmenting" or "accelerating" nerves thus discovered leave the spinal cord mainly by the roots of the second dorsal nerves, and enter the ganglion stellatum, whence they pass through the anterior and posterior loops of the annulus of Vieussens into the inferior cervical ganglion, from which they go, in the cardiac branches of the latter, to the heart.[2] Some of the cardiac fibres in the annulus pass directly thence to the cardiac plexus and do not enter the inferior cervical ganglion.

In the *rabbit*,[3] the course of the augmentor fibres is probably closely similar to that in the dog.

In the *cat*,[4] the augmentor nerves spring from the ganglion stellatum, and very rarely from the inferior cervical ganglion as well. The right cardiac sympathetic nerve communicates with the vagus.

The stimulation of the sympathetic chain in the *frog*, " between ganglion 1 and the vagus ganglion, and also stimulation of the chain between ganglia 2 and 3, causes marked acceleration and augmentation of the auricular and ventricular contractions. Stimulation between ganglia 3 and 4 produces no effect whatever upon the heart."[5] This experiment of Gaskell and Gadow's shows that augmentor fibres enter the sympathetic from the spinal cord along the ramus communicans of the third spinal nerve and pass upward in the sympathetic chain. In this animal the sympathetic chain, after dividing between the first and second ganglia to form the annulus of Vieussens, joins the trunk of the vagus between the united vagus and glosso-pharyngeal ganglia and the vertebral column (see Fig. 118). Here the sympathetic again divides, some of
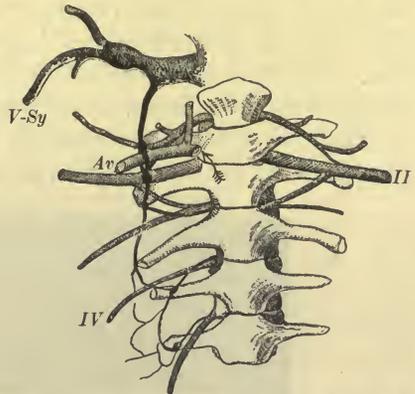
FIG. 118.—The cardiac sympathetic nerves in Rana temporaria (twice natural size): *V-Sy*, vago-sympathetic; *A.v*, arteria vertebralis; *II, IV*, second and fourth spinal nerves (Gaskell and Gadow, 1884).

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[1] von Bezold, 1866, p. 834; Bever and von Bezold, 1867, p. 227.

[2] Roy and Adami, 1892, p. 238; compare Schmiedeberg, 1871, p. 38, and Langley, 1893, p. 108; the latter states on p. 108 the results of Bever and von Bezold, 1867, Schmiedeberg, 1871, Boehm and Nussbaum, 1875, Stricker and Wagner, 1878, Bradford, 1889, and Bradford and Dean, 1889.

[3] Bever and von Bezold, 1867, p. 247; see remarks of Gaskell and Gadow, 1884, p. 370.

[4] Boehm, 1875, p. 260.   [5] Gaskell and Gadow, 1884, p. 369.

the fibres passing alongside the vagus into the cranial cavity, the rest accompany-
ing the vagus nerve peripherally. The augmentor nerves for the heart are
among the latter, for the stimulation of the intracranial vagus results in pure
inhibition,[1] while the stimulation of the vagus trunk after it is joined by the
sympathetic may give either inhibition or augmentation. We may say, there-
fore, that the augmentor nerves of the frog pass out of the spinal cord by the
third spinal nerve, through the ramus communicans of this nerve, into the
third sympathetic ganglion, up the sympathetic chain to the ganglion of the
vagus, and down the vagus trunk to the heart.

Stimulation of Augmentor Nerves.—The most obvious effect of the stim-
ulation of the augmentor nerves is an increase of from 7 to 70 per cent. in the
frequency of the heart-beat (see Fig. 119). The quicker the heart is beating
before the stimulation, the less marked is the acceleration. The absolute maxi-
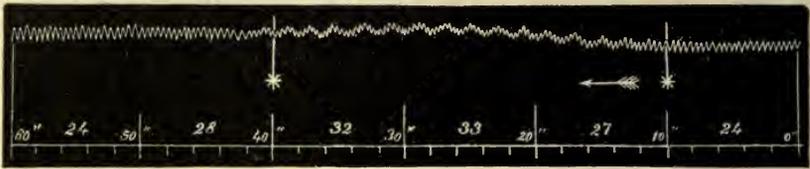
FIG. 119.—Curve of blood-pressure in the cat, recorded by a mercury manometer, showing the
increase in frequency of heart-beat from excitation of the augmentor nerves. The curve reads from
right to left. The augmentor nerves were excited during thirty seconds, between the two stars. The
number of beats per ten seconds rose from 24 to 33 (Boehm, 1875, p. 258).

mum of frequency is, however, independent of the frequency before stimulation.[2]
The maximum of acceleration is largely independent of the duration of stimula-
tion. The duration of stimulation and the duration of acceleration are not
related, a long stimulation causing no greater acceleration than a short one.[3]

The *force* of the ventricular beat is increased.[4] The ventricle is filled more
completely by the auricles, the volume of the ventricle being increased. The
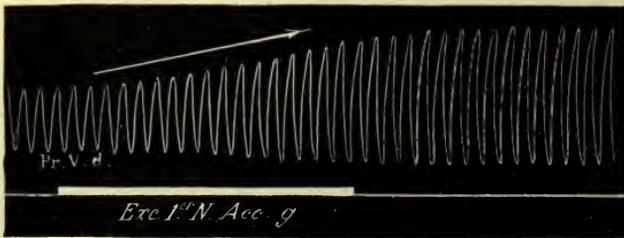
FIG. 120.—Increase in the force of the ventricular contraction (curve of pressure in right ventricle) from
stimulation of angmentor fibres. There is little or no change in frequency (Franck, 1890, p. 819).

output of the heart is raised.[5] There is no definite relation between the in-
crease of contraction volume or force of contraction and the increase in fre-
quency (see Fig. 120). Either may appear without the other, though this is

[1] Gaskell, 1884, p. 48.   [2] Boehm, 1875, p. 277.   [3] Baxt, 1877, p. 523.
[4] Heidenhain, 1882, p. 396; Gaskell, 1884, p. 47; 1886, p. 42; Mills, 1886, p. 554; Franck,
1890, p. 814; Roy and Adami, 1892, p. 242; Bayliss and Starling, 1892, p. 413.
[5] Roy and Adami, 1892, p. 240.

rare.[1] The simultaneous stimulation of the nerves of both sides does not give a greater maximum frequency than the stimulation of one nerve alone.[2]

The strength and the volume of the auricular contractions are also increased. The increase in volume is not due to a rise of pressure in the veins —in fact, the pressure falls in the veins—but to a change in the elasticity of the relaxed auricle, a lowering of its tonus. This change is not related to the increase in the force of the auricular contractions that stimulation of the augmentor nerves also causes. It varies much in amount and is less constantly met with than the change in force.[3] The changes in the ventricle and auricle probably account for the rise of blood-pressure in the systemic arteries and the fall in both systemic and pulmonary veins observed by Roy and Adami.[4]

The speed of the cardiac *excitation wave* is increased. Its passage across the auriculo-ventricular groove is also quickened, as is shown in the following experiment of Bayliss and Starling.[5] In the dog, the artificial excitation of the ventricle may cause the excitation wave to travel in a reverse direction, namely, from ventricle to auricle. If the ventricles are excited rhythmically and the rate of excitation is gradually increased, a limit will be reached beyond which the auricle no longer beats in response to every ventricular contraction. With intact vagi, a rate of 3 per second is generally the limit. If now the augmentor nerve is stimulated, the "block" is partially removed, and the auricle beats during and for a short time after the stimulation at the same rapid rate as the ventricle.

The *latent period* of the excitation is long. In the dog, about two seconds pass between the beginning of stimulation and the beginning of acceleration, and ten seconds may pass before the maximum acceleration is reached.[6] The after-effect may continue two minutes or more.[7] It consists of a weakening of the contractions and an increase in the difficulty with which the excitation wave passes from the auricle to the ventricle. The return to the former frequency is more rapid after short than after long stimulations.[8]

The *simultaneous stimulation* of the inhibitory and the augmenting nerves of the heart, either in the vagus or separately, causes, in warm-blooded animals, inhibition and not augmentation. The inhibition overcomes the augmentation,[9] but the vagus effect is diminished nevertheless. The acceleration that is seen after the stimulation of the vagus is due to the after-effect of the stimulation of accelerating fibres in the vagus.

The simultaneous stimulation of the augmentors and the vagi, the strength of the current being sufficient to stop the auricular contractions, causes acceleration of the ventricular contractions.[10]

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[1] Franck, 1890, p. 819; Roy and Adami, 1892, p. 240. [2] Franck, 1880, p. 85.

[3] Roy and Adami, 1892, p. 240. [4] *Ibid.*

[5] Bayliss and Starling, 1892, p. 415. [6] Baxt, 1877, p. 529.

[7] von Bezold and Bever, 1867, p. 245; Schmiedeberg, 1870, p. 136; 1871, p. 43; Boehm, 1875, p. 273. [8] Baxt, 1877, p. 536.

[9] Bowditch, 1873, p. 273; Baxt, 1875, p. 204; Boehm, 1875, p. 278.

[10] Bayliss and Starling, 1892, p. 414. For further discussion of the effects of simultaneous stimulation, see Meltzer, 1892, p. 376.

OTHER CENTRIFUGAL HEART-NERVES.

In the vago-sympathetic trunk and the annulus of Vieussens fibres pass to the heart that cannot be classed either with the vagus or the augmentor nerves. The evidence for their existence is furnished by Roy and Adami's observation that when the intracardiac vagus mechanism is acting strongly, so that the auricles are more or less completely arrested, the stimulation of the vago-sympathetic trunk sometimes causes a decided increase in the force both of the ventricles and the auricles, usually accompanied by an acceleration of the rhythm of the heart. These changes are too rapidly produced to be augmentor effects.[1]

Centrifugal inhibitory nerves have been found as an anomaly in the right depressor nerve of a rabbit.[2]

Pawlow[3] divides the inhibitory and augmentor nerves into four classes—(1) nerves inhibiting the frequency of the beat, (2) nerves inhibiting the force of the contraction, (3) nerves augmenting frequency, and (4) nerves augmenting force. The origin of this subdivision of the two groups generally recognized was the observation that, in certain stages of convallaria poisoning, the excitation of the vagus in the neck—all the branches of the nerve except those going to heart and lungs being cut—reduced the blood-pressure without altering the frequency of the beat. Further researches showed that the stimulation of branch 3 (Fig. 121) even in unpoisoned animals reduced the blood-pressure independently of the variable alteration simultaneously produced in the pulse-rate. Stimulation of branch 5 produced an acceleration of the heart-beat without increase of blood-pressure. Other branches brought about rise of pressure without acceleration, and increased discharge by the left ventricle without alteration in the pulse-rate.

FIG. 121.—Scheme of the centrifugal nerves of the heart according to Pawlow: 1, vago-sympathetic nerve; 2, upper inner branch; 3, strong inner branch; 4, lower inner branch; 5, upper and lower outer branches; 6, ganglion stellatum; 7, annulus of Vieussens; 8, middle (inferior) cervical ganglion; 9, recurrent laryngeal nerve.

These results are supported further by Wooldridge's observation that excitation of the peripheral ends of certain nerves on the posterior surface of the ventricle raised the blood-pressure without modifying the frequency of contraction,[4] and by Roy and Adami's demonstration that certain branches of the first thoracic ganglion lessen the force of the cardiac contraction without influencing its rhythm.[5] But the matter is as yet far from certain.

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[1] Roy and Adami, 1892, p. 249.
[2] Hering, 1894, p. 78.
[3] Pawlow, 1887, p. 510.
[4] Wooldridge, 1883, p. 537.
[5] Roy and Adami, 1892, p. 246.

The Centripetal Nerves of the Heart.

The Ventricular Nerves.—When the mammalian heart is freed from blood by washing it out with normal saline solution and the ventricle is painted with pure carbolic acid, liquefied by warming, numerous nerves appear as white threads on a brown background. They are non-medullated, form many plexuses, and run beneath the pericardium obliquely downward from the base to the apex of the ventricle. They may be traced to the cardiac plexus. These fibres are not centrifugal branches of the vagus or the augmentor nerves, for the characteristic effects of vagus and augmentor stimulation are seen after section of the nerves in question. The stimulation of their peripheral ends, moreover, the fibre being carefully dissected out from the subpericardial tissue, cut across, and the cut end raised on a thread in the air, is without effect on the blood-pressure and pulse-rate. The stimulation of the central stumps of these nerves, on the contrary, is followed by changes both in the blood-pressure and the pulse, showing that they carry impulses from the heart to the cardiac centres in the central nervous system, or perhaps, according to the views of some recent investigators, to peripheral ganglia, thus modifying the action of the heart reflexly.[1]

Sensory Nerves of the Heart.—The stimulation of intracardiac nerves by the application of acids and other chemical agents to the surface of the heart causes various reflex actions, such as movements of the limbs. The afferent nerves in these reflexes are the vagi, for the reflex movements disappear when the vagi are cut.[2] On the strength of these experiments the vagus has been believed to carry sensory impressions from the heart to the brain. Direct stimulation of the human heart, in cases in which a defect in the chest-wall has made the organ accessible, give evidence of a dim and very limited recognition of cardiac events—for example, the compression of the heart.[3]

Vagus.—The stimulation of the central end of the cut vagus nerve, the other vagus being intact, causes a slowing of the pulse-rate. The section of the second vagus causes this retardation of the pulse to disappear, indicating that the stimulation of the central end of the one affects the heart reflexly through the agency of the other vagus. The blood-pressure is simultaneously affected, being sometimes lowered and sometimes raised, the difference seeming to depend largely on the varying composition of the vagus in different animals and in different individuals of the same species.[4] The stimulation of the pulmonary branches, by gently forcing air into the lungs, loud speaking, singing, etc., is said to increase the frequency of the heart-beat.[5] Yet the chemical stimulation of the mucous membrane of the lungs is alleged to slow the pulse-

[1] Wooldridge, 1883, pp. 523, 529, 539; see also Lee, 1849, p. 43.
[2] Budge, 1846, p. 588; Goltz, 1863, p. 5; Gurboki, 1872, p. 289; Franck, 1880, p. 382.
[3] v. Ziemssen, 1882, p. 297; Nothnagel, 1891, p. 209.
[4] See Franck, 1880, p. 281; v. Bezold, 1863, p. 281; Dreschfeld, 1867, p. 326; Aubert and Roever, 1868, p. 211; Kowalewsky and Adamük, 1868, p. 546; Cybulski and Wartanow, 1883; Rey and Aducco, 1887, p. 188; Arendt, 1890, p. 11; Roy and Adami, 1892, p. 251.
[5] Hering, 1871; Sommerbrodt, 1881, p. 602.

rate and lower the blood-pressure.[1]   Observers differ as to the results of stim-
ulation of the central end of the laryngeal branches of the vagus on the pulse-
rate and blood-pressure.[2]

Depressor Nerve.—The earlier stimulations of the nerves that pass
between the central nervous system and the heart, with the exception of the
vagus, altered neither the blood-pressure nor the pulse-rate. Ludwig and Cyon[3]
suspected that the negative results were owing to the fact that the stimulations
were confined to the end of the cut nerve in connection with the heart.   Some
of the nerves, they thought, should carry impulses from the heart to the brain,
and such nerves could be found only by stimulation of the brain end of the
cut nerve. They began their research for these afferent nerves with the branch
which springs from the rabbit's vagus high in the neck and passes downward
to the ganglion stellatum.   Their suspicion was at once confirmed.   The stimu-
lation of the central end of this nerve, called by Ludwig and Cyon the depres-
sor, caused a considerable fall of the blood-pressure.

The depressor nerve arises in the rabbit by two roots, one of which comes
from the trunk of the vagus itself, the other from a branch of the vagus, the
superior laryngeal nerve.   Frequently the origin is single; in that case it is
usually from the nervus laryngeus.[4]   The nervus depressor runs in company
with the sympathetic nerve to the chest, where communications are made with
the branches of the ganglion stellatum.

The stimulation of the peripheral end of the depressor nerve is without
effect on the blood-pressure and heart-beat.   The stimulation of the central
end, on the contrary, causes a gradual fall of the general blood-pressure to the
half or the third of its former height.   After the stimulation is stopped, the
blood-pressure returns gradually to its previous level.

Simultaneously with the fall in blood-pressure a lessening of the pulse-rate
sets in. The slowing is most marked at the beginning of stimulation, and after
rapidly reaching its maximum gives way gradually until the rate is almost
what it was before the stimulation began.   After stimulation the frequency is
commonly greater than previous to stimulation.

After section of both vagi, the stimulation of the depressor causes no change
in the pulse-rate, but the blood-pressure falls as usual.   The alteration in fre-
quency is therefore brought about through stimulation of the cardiac inhibitory
centre, acting on the heart through the vagi.   The experiment teaches, further,
that the alteration in pressure is not dependent on the integrity of the vagi.

Poisoning with curare paralyzes all motor mechanisms except the heart and
the muscles of the blood-vessels.   Yet curare-poisoning does not affect the
result of depressor stimulation.   The cause of the fall in blood-pressure must
be sought then either in the heart or the reflex dilatation of the blood-vessels.
It cannot be in the heart, for depressor stimulation lowers the blood-pressure
after all the nerves going to the heart have been severed.   It must therefore

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[1] Franck, 1880, p. 378.   [2] Aubert and Roever, 1868, p. 241; Franck, 1880, p. 357.
[3] Ludwig and Cyon, 1866, p. 128.
[4] Tschirwinsky, 1896, p. 778, gives a somewhat different account.

lie in the blood-vessels. Ludwig and Cyon knew that the dilatation of the intestinal vessels could produce a great fall in the blood-pressure and turned at once to them. Section of the splanchnic nerve caused a dilatation of the abdominal vessels and a fall in the blood-pressure. Stimulation of the peripheral end of the cut splanchnic caused the blood-pressure to rise even beyond its former height. If now the depressor lowers the blood-pressure chiefly by affecting the splanchnic nerve reflexly, the stimulation of the central end of the depressor after section of the splanchnic nerves ought to have little effect on the blood-pressure. This proved to be the case. The depressor, therefore, reduces the blood-pressure chiefly by lessening the tonus of the vessels governed by the splanchnic nerve, thus allowing their dilatation and in consequence lessening the peripheral resistance.

It has already been said that the depressor fibres pass from the heart to the vaso-motor mechanism in the central nervous system. The cardiac fibres are probably stimulated when the heart is overfilled through lack of expulsive force or through excessive venous inflow, and, by reducing the peripheral resistance, assist the engorged organ to empty itself.

The depressor nerve is not in continual action; it has no tonus; for the section of both depressor nerves causes no alteration in the blood-pressure.

The many successors of Cyon and Ludwig have added relatively few important facts to their extraordinary investigation.

Sewall and Steiner [1] have obtained in some cases a permanent rise in blood-pressure following section of both depressors, yet they hesitate to say that the depressor exercises a tonic action.

Spallita and Consiglio [2] have stimulated the depressor before and after the
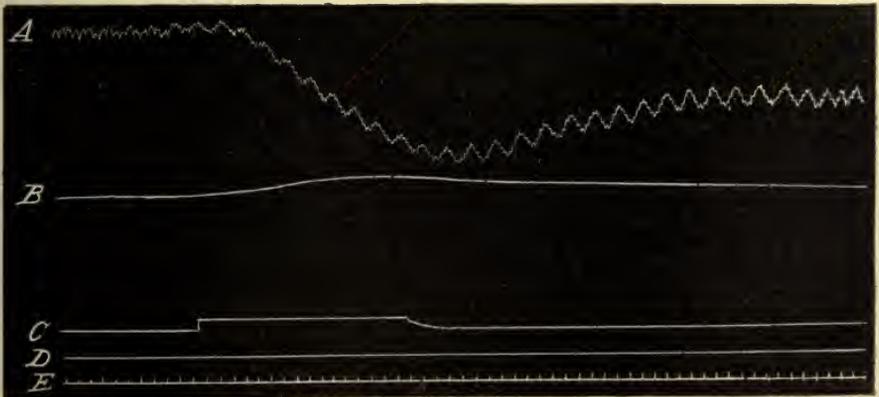
Fig. 122.—Showing the fall in blood-pressure and the dilatation of peripheral vessels from stimulation of the central end of the depressor nerve (Bayliss): *A*, curve of blood-pressure in the carotid artery; *B*, volume of hind limb, recorded by a plethysmograph; *C*, electro-magnet line, in which the elevation shows the time of stimulation of the nerve; *D*, atmospheric pressure-line; *E*, time in seconds.

section of the spinal accessory nerve near its junction with the vagus. They find that after section of the spinal accessory, the stimulation of the depressor

[1] Sewall and Steiner, 1885, p. 168.   [2] Spallita and Consiglio, 1892, p. 42.

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does not affect the pulse, whence they conclude that the depressor fibres that affect the blood-pressure are separate from those that affect the rate of beat, the latter being derived from the spinal accessory nerve.

A recent study by Bayliss[1] brings out several new facts. If a limb is placed in Mosso's plethysmograph and the central end of the depressor stimulated, the volume of the limb increases, showing an active dilatation of the vessels that supply it. The latent period of this dilatation varies greatly. The vessels of the skin play a large part in its production. A similar local action is seen on the vessels of the head and neck (see Fig. 122).

The depressor fibres vary much in size in different animals. When the nerve is small, a greater depressor effect can be obtained by stimulating the central end of the vagus than from the depressor itself. But the course of the fall is different in the two cases. With the depressor, the fall is maintained at a constant level during the whole excitation, however long it lasts, whereas in the case of the vagus the pressure very soon returns to its original height although the excitation still continues. Bayliss believes, therefore, that there is a considerable difference between the central connections of the depressor nerve itself and the depressor fibres sometimes found in other nerves.

The left depressor nerve usually produces a greater fall of pressure than the right. The excitation of the second nerve during the excitation of the first produces a greater fall than the excitation of one alone.

The fibres of the depressor, in part at least, end in the wall of the ventricle.[2] A similar nerve has been demonstrated in the cat,[3] horse,[4] dog,[5] sheep,[6] swine,[7] and in man.[8]

Sensory Nerves.—The first and usually the only effect of the stimulation of the central end of a mixed nerve like the sciatic, according to Roy and Adami,[9] is an increase in the force and the frequency of the heart-beat. Other observers[10] have sometimes found quickening and sometimes slowing of the pulse-rate, so that sensory nerves, as Tigerstedt[11] suggests, appear to affect both the inhibitory and the augmenting heart-nerves. When a sensory nerve is weakly excited the augmentor effect predominates, when strongly excited the inhibitory. A well-known demonstration of the reflex action of the sensory nerves on the heart is seen in the slowing of the rabbit's heart when the animal

[1] Bayliss, 1893, p. 304.   [2] Kazem-Beck, 1888, p. 329.
[3] Bernhardt, 1868, p. 5; Aubert and Roever, 1868, p. 214; Kowalewsky and Adamük, 1868, p. 545; Roever, 1869, p. 68; Kazem-Beck, 1888, p. 331.
[4] Bernhardt, 1868, p. 5; Cyon, 1870, p. 262; Finkelstein, 1880, p. 350.
[5] Roever, 1869, p. 71; Langenbacher, 1877; Kreidmann, 1878, p. 411; Finkelstein, 1880, p. 248; Kazem-Beck, 1888, p. 332.
[6] Kriedmann, 1878, p. 407.
[7] Langenbacher, 1877; Kazem-Beck, 1888, p. 335; the latter describes also (p. 338) a depressor nerve in cold-blooded animals; compare Gaskell and Gadow, 1885, p. 362.
[8] Bernhardt, 1868, p. 5; Kreidmann, 1878, p. 408; Finkelstein, 1880, p. 249; Békésy, 1888.
[9] Roy and Adami, 1892, p. 254.
[10] Lovén, 1866, p. 5; Bernard, 1858, p. 291; Asp, 1867, p. 173; Tranck, 1876, p. 246; Simanowsky, 1881.   [11] Tigerstedt, 1893, p. 287.

is made to inhale chloroform. The superior laryngeal and the trigeminus nerves, especially the latter, convey the stimulus to the nerve-centres.[1]

The stimulation of the *nerves of special sense*, optic, auditory, olfactory and glosso-pharyngeal nerves, also sometimes slows and sometimes quickens the heart.[2]

Sympathetic.—The reflex action of the sympathetic nerve upon the heart is well shown by the celebrated experiment of F. Goltz.[3] In a medium-sized frog, the pericardium was exposed by carefully cutting a small window in the chest-wall. The pulsations of the heart could be seen through the thin peri-cardial membrane. Goltz now began to beat upon the abdomen about 140 times a minute with the handle of a scalpel. The heart gradually slowed, and at length stood still in diastole. Goltz now ceased the rain of little blows. The heart remained quiet for a time and then began to beat again, at first slowly and then more rapidly. Some time after the experiment, the heart beat about five strokes in the minute faster than before the experiment was begun. The effect cannot be obtained after section of the vagi.

Bernstein[4] found that the afferent nerves in Goltz's experiment were branches of the abdominal sympathetic, and discovered that the stimulation of the cen-tral end of the abdominal sympathetic in the rabbit was followed also by reflex inhibition of the heart.

The stimulation of the central end of the splanchnic produces a reflex rise of blood-pressure and, perhaps secondarily, a slowing of the heart.[5] In some cases acceleration has been observed.[6] According to Roy and Adami splanch-nic stimulation sometimes produces a combination of augmentor and vagus effects, the augmentation appearing during stimulation and giving place abruptly to well-marked inhibitory slowing at the close of stimulation.[7]

The results of stimulating various abdominal viscera have been studied by Mayer and Pribram. One of the most interesting of the reflexes observed by them was the inhibition of the heart called forth by dilating the stomach.[8]

The stimulation of the cervical sympathetic does not give any very constant results on the action of the heart.[9]

B. The Centres of the Heart-nerves.

Inhibitory Centre.—It has been already mentioned that the brothers Weber[10] localized the cardiac inhibitory centre in the medulla oblongata. The efforts to fix the exact location of the centre by stimulation of various parts, either mechanically, by thrusting fine needles into the medulla,[11] or electrically,

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[1] Dogiel, 1866, p. 236; Kratschmer, 1870, p. 159; Franck, 1876, p. 227; Simanowsky, 1881.
[2] Couty and Charpentier, 1877, p. 563.   [3] Goltz, 1863, p. 11.
[4] Bernstein, 1863, p. 818; 1864, pp. 617, 642.   [5] Asp, 1867, p. 150.
[6] v. Bezold, 1863, p. 252; Asp, 1867, p. 172; Sabbatini, 1891, p. 219.
[7] Roy and Adami, 1892, p. 258.
[8] Mayer and Pribram, 1872, p. 107; Simanowsky, 1881.
[9] Bernstein, 1864, p. 630; Aubert and Roever, 1868, p. 240; 1869, p. 95; Bernstein, 1868, p. 601.   [10] Weber, 1846, p. 45.
[11] Eckhard, 1878, p. 187; Klug, 1880, p. 516; Laborde, 1888, p. 400.

cannot inspire great confidence because of the difficulty of distinguishing between the results that follow the excitation of a nerve-path from or to the centre and those following the excitation of the centre itself. According to Laborde, who also used this method, the cardiac inhibitory centre is situated at the level of the mass of cells known as the accessory nucleus of the hypoglossus and the mixed nerves (vagus, spinal accessory, glosso-pharyngeal).[1]

The localization of the centre by the method of successive sections is perhaps more trustworthy. Franck[2] has found that the separation of the bulb from the spinal cord cuts off the reflexes called forth by nerves that enter the spinal cord, while leaving undisturbed the reflex produced by stimulation of the trigeminus nerve.

On the whole, there seems to be no doubt that the cardiac inhibitory centre is situated in the bulb.

Tonus of Cardiac Inhibitory Centre.—The cardiac inhibitory centre is probably always in action, for when the vagus nerves are cut, the heart-beat becomes more frequent. The source of this continued or "tonic" activity may lie in the continuous discharge of inhibitory impulses created by the liberation of energy in the cell independent of direct external influences, or the cells may be discharged by the continuous stream of afferent impulses that must constantly play upon them from the multitude of afferent nerves. This latter theory, the conception of a reflex tonus, is made probable by the observations that section of the vagi does not increase the rate of beat after the greater part of the afferent impulses have been cut off by division of the spinal cord near its junction with the bulb,[3] and that the sudden decrease in the number of afferent impulses caused by section of the splanchnic nerve quickens the pulse-rate.[4]

Irradiation.—The slowing of the rate of beat observed chiefly during the expiratory portion of respiration disappears after the section of both vagus nerves. The slowing may perhaps be due to the stimulation of the cardiac inhibitory centre by irradiation from the respiratory centre.[5]

Origin of Cardiac Inhibitory Fibres.—Since the researches of Waller[6] and others, it has been generally believed that the cardiac inhibitory fibres enter the vagus from the spinal accessory nerve, for the reason that cardiac inhibition was not secured in animals in which the fibres in the vagus derived from the spinal accessory nerve were made to degenerate by tearing out the latter before its junction with the vagus. These results have lately been called in question by Grossmann.[7] The method employed by his predecessors, according to him, probably involved the destruction of vagus roots as well as those of the spinal accessory. Grossmann finds that the stimulation of the spinal accessory nerve before its junction with the vagus does not inhibit the heart. Nor does inhibition follow the stimulation of the bulbar roots supposed to be contributed to the mixed nerve by the spinal accessory.

[1] Laborde, 1888, p. 415.   [2] Franck, 1876, p. 255.   [3] Bernstein, 1864, p. 654.
[4] Asp, 1867, p. 136.   [5] Laulanié, 1893, p. 723.
[6] Waller, 1856, p. 420; Schiff, 1858; Heidenhain, 1865, p. 109; Gianuzzi, 1872; Franck, 1876, p. 264.   [7] Grossmann, 1895, p. 6.

Augmentor Centre.—The situation of the centre for the augmentor nerves of the heart is not definitely known, although from analogy it seems probable that it will be found in the bulb. That this centre is constantly in action is indicated by the lowering of the pulse-rate after section of the vagi followed by the bilateral extirpation of the inferior cervical and first thoracic ganglia. The division of the spinal cord in the upper cervical region after the section of the vagi has the same effect.[1] Vagus inhibition, moreover, is said to be more readily produced after section of the augmentor nerves.[2]

McWilliam[3] has remarked that the latent period and the character of the acceleration often accompanying the excitation of afferent nerves may differ entirely from the characteristic effects of the excitation of augmentor nerves. The stimulation of the latter is followed by a long latent period, after which the rate of beat gradually increases to its maximum and, after excitation is over, as gradually declines. The excitation of an afferent nerve, on the contrary, causes often, with almost no latent period, a remarkably sudden acceleration, that reaches at once a high value and often suddenly gives way to a slow heart-beat. These facts seem to show that reflex acceleration of the heart-beat is due to changes in the cardiac inhibitory centre, and not to augmentor excitation. This view is strengthened by the fact that if the augmentor nerves are cut, the vagi remaining intact, the stimulation of afferent fibres, for example in the brachial nerves, can still cause a marked quickening of the pulse-rate. In short, the action of afferent nerves upon the rate of beat is essentially the same, according to this observer, whether the augmentor nerves are divided or intact.

Roy and Adami[4] believe that the stimulation of afferent nerves, such as the sciatic or the splanchnic, excites both augmentor and vagus centres. The augmentor centre is almost always the more strongly excited of the two, so that augmentor effects alone are usually obtained.

Action of Higher Parts of the Brain on Cardiac Centres.—Repeated efforts have been made to find areas in the cortex of the brain especially related to the inhibition or augmentation of the heart, but with results so contradictory as to warrant the conclusion that the influence on the heart-beat of the parts of the brain lying above the cardiac centres does not differ essentially from that of other organs peripheral to those centres.[5]

Voluntary control of the heart, by which is meant the power to alter the rate of beat by the exercise of the will, is impossible except as a rare individual peculiarity, commonly accompanied by an unusual control over muscles, such as the platysma, not usually subject to the will. Cases are described by Tarchanoff[6] and Pease,[7] in which acceleration of the beat up to twenty-seven

[1] Tschirjew, 1877, p. 164; Stricker and Wagner, 1878, p. 370.

[2] Sustschinsky, 1868, p. 164.   [3] McWilliam, 1893, p. 472.

[4] Roy and Adami, 1892, p. 260.

[5] See Danilewsky, 1875, p. 130; Bochefontaine, 1876, p. 140; 1883, p. 33; Balogh, 76; Eckhard, 1878, p. 185; Bechterew and Mislawsky, 1886, pp. 193, 416; Franck, 1887, p. 162.

[6] Tarchanoff, 1884, p. 113.

[7] Pease, 1889, p. 525.

in the minute was produced, together with increase of blood-pressure, from vaso-constrictor action. The experiments are dangerous.

Peripheral Reflex Centres.—It is now much discussed whether the peripheral ganglia can act as centres of reflex action. According to Franck[1] the excitation of the central stump of the divided left anterior limb of the annulus of Vieussens is transformed within the first thoracic ganglion, isolated from the spinal cord by section of its ramus communicans, into a motor impulse transmitted by the posterior limb of the annulus. This motor impulse causes, independently of the bulbo-spinal centres, a reflex augmentation in the action of the heart, and a reflex constriction of the vessels in the external ear, the submaxillary gland, and the nasal mucous membrane. This experiment, in conjunction with the facts in favor of other sympathetic ganglia acting as reflex centres,[2] seems to demonstrate that some afferent impulses are transformed in the sympathetic cardiac ganglia into efferent impulses modifying the action of the heart. If this conclusion is confirmed by future investigations it will profoundly modify the views now entertained regarding the innervation of the heart.

Intra-ventricular Centre.—Kronecker and Schmey,[3] finding that puncture of the inter-ventricular septum at the junction of the upper and middle thirds often caused arrest of the heart with fibrillary contractions, have set up the hypothesis of a co-ordinating centre at that point, essential to the co-ordinated contractions of the ventricle. Their results are possibly due to inhibition ;[4] certainly they are not to be explained by the destruction of a co-ordinating centre. The anatomical basis for such a conception is wanting, careful search having failed to reveal any ganglion-cells in the locality in question,[5] and the heart has been observed to beat for hours and even days after the cardiac tissue of this part of the septum had been destroyed by infarction, caused by the ligation of its nutrient arteries.[6]

The *experiments of Stannius*, published in 1852, have been the starting-point of a very great number of researches on the innervation of the frog's heart. Stannius observed, among other facts, that the heart remained for a time arrested in diastole when a ligature was tied about the heart precisely at the junction of the sinus venosus with the right auricle. No sufficient explanation of this result has yet been given, nor is one likely to be found until the innervation of the heart is better understood. Stannius[7] further

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[1] Franck, 1894, p. 721.

[2] See Wertheimer, 1890, p. 519; Skabitschewsky, 1891, p. 156; Langley and Anderson, 1893, p. 435.

[3] Kronecker and Schmey, 1884, p. 89; Sée and Gley, 1887, p. 827; the latter could not get arrest in 11 out of 14 dogs.

[4] Knoll, 1894, p. 312, observed fibrillation of the auricles in consequence of vagus stimulation; escape of current into the heart was guarded against.

[5] Krehl and Romberg, 1892, p. 54.

[6] Porter, 1893, p. 366; for the effect of wounds of the heart upon its rhythm, see Rodet and Nicolas, 1896, p. 167.

[7] A review of the Stannius literature is given by Tigerstedt, *Physiologie des Kreislaufes*, 1893, p. 196.

observed that after the ligature just described had been drawn tight, thus arresting the heart, the placing of a second ligature around the heart at the junction of the auricle and ventricle caused the latter to begin to beat again, while the auricle remained at rest. This second ligature, it is generally admitted, stimulates the ganglion of Bidder, and the ventricle responds by rhythmic contractions to the constant excitation thus produced. Loosening the ligature and so interrupting the excitation stops the ventricular beat.[1]

PART III.—THE NUTRITION OF THE HEART.

The cells of which the heart-wall are composed are nourished by contact with a nutrient fluid. In hearts consisting of relatively few cells no special means of bringing the nutrient fluid to the cells is required. The walls of the minute globular heart of the small crustacean *Daphnia*, for example, are composed of a single layer of cells, each of which is bathed by the fluid which the heart pumps. In larger hearts with thicker walls only the innermost cells could be fed in this way. Special means of distributing the blood throughout the substance of the organ are necessary here.

Passages in the Frog's Heart.—In the frog this distribution is accomplished chiefly through the irregular passages which go out from the cavities of the heart between the muscle-bundles to within even the fraction of a millimeter of the external surface.[2] These passages vary greatly in size. Many are mere capillaries. They are lined by a prolongation of the endothelium of the heart. Filled by every diastole and emptied by every systole, they do the work of blood-vessels and carry the blood to every part of the cardiac muscle.

Henri Martin[3] describes a coronary artery in the frog, analogous to the coronary arteries of higher vertebrates. This artery supplies a part of the auricles and the upper fourth of the ventricle.

In the rabbit, cat and dog, and in man a well-developed system of cardiac vessels exists, the coronary arteries and veins. Their distribution in the dog deserves especial notice, because the physiological problems connected with these vessels have been studied chiefly in this animal.

Coronary Arteries in the Dog.—In the dog the coronary arteries and their larger branches lie upon the surface of the heart, covered as a rule only by the pericardium and a varying quantity of connective tissue and fat. The left coronary artery is extraordinarily short. A few millimeters after its origin from the aorta it divides into the large ramus circumflex and the descendens, nearly as large. The former runs in the auriculo-ventricular furrow around the left side of the heart to the posterior surface, ending in the posterior inter-ventricular furrow. The left auricle and the upper anterior and the posterior portion of the left ventricle are supplied by this artery. The descendens runs downward in the anterior inter-ventricular furrow to the apex. Close to its origin the descendens gives off the arteria septi, which at once enters the

[1] Goltz, 1861, p. 201. [2] Engelmann, 1874, p. 11. [3] Martin, 1893, p. 754; 1894, p. 46.

inter-ventricular septum and passes, sparsely covered with muscle-bundles, obliquely downward and backward on the right side of the septum. The descendens in its farther course gives off numerous branches to the left ventricle and the anterior part of the septum. Only a few small branches go to the right ventricle. Thus the descendens supplies the septum and the inferior anterior part of the left ventricle. The right coronary artery, imbedded in fat, runs in the right auriculo-ventricular groove around the right side of the heart, supplying the right auricle and ventricle. It is a much smaller artery than either the circumflex or descendens. Each coronary artery keeps to its own boundaries and does not, in the dog, pass into the field of another artery, as sometimes happens in man.[1]

Terminal Nature of Coronary Arteries.—The coronary arteries in the dog, as in man, are terminal arteries, that is, the anastomoses which their branches have with neighboring vessels do not permit the making of a collateral circulation. Their terminal nature in the human heart is shown by the formation of infarcts in the areas supplied by arteries which have been plugged by embolism or thrombosis. That part of the heart-wall supplied by the stopped artery speedily decays. The bloodless area is of a dull white color, often faintly tinged with yellow ; rarely it is red, being stained by hæmoglobin from the veins of neighboring capillaries. The cross section is coarsely granular. The nuclei of the muscle-cells have lost their power of staining. The muscle-cells are dead and connective tissue soon replaces them.[2] This loss of function and rapid decay of cardiac tissue would not take place did anastomoses permit the establishment of collateral circulation between the artery going to the part and neighboring arteries. The terminal nature of the coronary arteries in the dog has been placed beyond doubt by direct experiment. It is possible to tie them and keep the animal alive until a distinct infarct has formed.[3]

The objection that one of the coronary arteries can be injected from another,[4] and that therefore they are not terminal, is based on the incorrect premise that terminal arteries cannot be thus injected, and has no weight against the positive evidence of the complete failure of nutrition following closure. The passage of a fine injection-mass from one vascular area to another proves nothing concerning the possibility of the one area receiving its blood-supply from the other. Such supply is impossible if the resistance in the communicating vessels is greater than the blood-pressure in the smallest branches of the artery through which the supply must come. It is the fact of this high resistance, due to the small size of the communicating branches, which makes the artery " terminal." This condition of high resistance is really present during life, or infarction could not take place.

The terminal nature of the coronary arteries is of great importance with regard to the part taken by them in the nutrition of the heart. Being ter-

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[1] Cohnheim and v. Schulthess-Rechberg, 1881, p. 511.

[2] See also the description by Kolster, 1893, p. 14, of the infarctions produced experimentally in the dog's heart.

[3] Kolster, 1893, p. 14 ; Porter, 1893, p. 366.   [4] Michaelis, 1894, p. 289.

minal, their experimental closure enables us to study the effects of the sudden stopping of the blood-supply (ischæmia) of the heart muscle upon the action of the heart.

Results of Closure of the Coronary Arteries.—The sudden closure of one of the large coronary branches in the dog has as a rule either no effect upon the action of the heart beyond occasional and transient irregularity,[1] or is followed after the lapse of seconds, or of minutes, by the arrest of the ventricular stroke, the ventricle falling a moment later into the rapid, fluttering,

FIG. 123.—*A*, curve of intra-ventricular pressure, written by a manometer connected with the interior of the left ventricle; *B*, atmospheric pressure; *C*, time in two-second intervals. At the first arrow the ramus circumflexus of the left coronary artery was ligated; at the second arrow the heart fell into fibrillary contractions. The lessening height of the curve shows the gradual diminution of the force of contraction after ligation. The rise of the lower line of the curve above the atmospheric pressure indicates a rise of intra-ventricular pressure during diastole. The small elevations in the pressure-curve after the second arrow are caused by the left auricle, which continued to beat after the arrest of the ventricle (Porter, 1893).

undulatory movements known as fibrillary contractions and produced by the inco-ordinated, confused shortenings of individual muscle-cells, or groups of cells. The auricles continue to beat for a time, but the power of the ventricles to execute co-ordinated contractions is lost.

The Frequency of Arrest.—The frequency with which closure is followed by ventricular arrest depends on at least two factors—namely, the size of the artery ligated and the irritability of the heart. That the size of the artery is of influence appears from a series of ligations performed on dogs, arrest being never observed after ligation of the arteria septi alone, rarely observed (14 per cent.) with the right coronary artery, more frequently (28 per cent.) with the descendens, and still more frequently (64 per cent.) with the arteria circumflexa.[2] The irritability of the heart is an important factor. In animals cooled by long artificial respiration, or by section of the spinal cord at its junction with the bulb, the ligation of the descendens arrests the heart less frequently than in vigorous animals which have been operated upon quickly. The frequency of arrest is increased by the use of morphia and curare.[3]

Changes in the Heart-beat.—Ligation destined to arrest the heart is followed almost immediately by a continuous fall in the intra-ventricular pressure during systole and a gradual rise in the pressure during diastole (see Fig. 123). The contraction and relaxation of the ventricle are often slowed. The force of the ventricular stroke is diminished. As arrest draws near, irregularities in the force of the ventricular beat are seldom absent.[4] The frequency of beat is sometimes unchanged throughout, but is usually diminished toward the end;

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[1] The changes produced by subsequent degeneration are not considered here.
[2] Porter, 1893, p. 131.   [3] *Ibid.*, 1896, p. 49.   [4] *Ibid.*, 1893, p. 133.

FIG. 124.—Showing fall in arterial pressure and diminished output of left ventricle in consequence of the ligation of the circumflex artery. The curve reads from left to right. It is one-half the original size. The upper curve is the pressure in the carotid artery. The unbroken line is atmospheric pressure. The next curve is the measurement of the outflow from the left ventricle, each rise and each fall indicating the passage of 50 c.cm. of blood into the aorta. The lower line is a time-curve in seconds. At * the circumflex artery was ligated (Porter, 1896, p. 51).

occasionally the frequency is increased. Both ventricles as a rule cease to beat at the same instant. The work done by the heart, measured by the blood thrown into the aorta in a unit of time, is lessened by ligation when followed by arrest[1] (see Fig. 124).

The Exciting Cause of Arrest.—There are two opinions concerning the exciting cause of the changes following closure of a coronary artery, some investigators holding for anæmia and others for mechanical injury of the cardiac muscle or its nerves in the operation of ligation. The latter base their claim on the frequent failure of ligation of even a main branch to stop the heart; on the fact that the heart of the dog has been seen to beat from 115 to 150 seconds after the blood-pressure in the aorta was so far reduced, by clamping the auricle and opening the carotid artery, as to make a continuance of the coronary circulation very improbable;[2] on the revival of the arrested heart by the injection of defibrinated blood into the coronary arteries from the aorta, by which means the dog's heart and even the human heart has been made to beat again many minutes after the total arrest of the circulation,[3]—it being assumed, incorrectly, that the dog's heart cannot be made to beat after arrest with fibrillary contractions; and, finally, on the arrest with fibrillary contractions which some experimenters have caused by mechanical injury to the heart.[4]

To sum up, the argument in favor of explaining arrest with fibrillary contractions simply by the mechanical injury done the heart in the process of ligation consists of two propositions: first, that anæmia without mechanical injury does not cause arrest with fibrillary contractions; and second, that mechanical injury without anæmia does cause arrest.

Against the second of these propositions must be placed the extreme infrequency of arrest from mechanical injuries. In more than one hundred

[1] Porter, 1896, p. 52.
[2] Tigerstedt, 1895, p. 87; Michaelis, 1894.
[3] Langendorff, 1895, p. 320; Hédon and Gilis, 1892, p. 760.   [4] Martin and Sedgwick, 1882, p. 168.

ligations Porter[1] observed not a single arrest in consequence of laying the artery bare and placing the ligature ready to be drawn, the only effect of the mechanical procedure being an occasional slight irregularity in force. Ligation of the periarterial tissues in ten dogs, the artery itself being excluded from the ligature, directly injured both muscular and nervous substance, but was only once followed by arrest.[2] Nor does arrest follow the ligation of a vein, although the mechanical injury is possibly as great as in tying an artery. The direct stimulation of the superficial ventricular nerves exposed to injury in the operation of ligation does not produce the effects that appear after the ligation of coronary arteries.[3]

Against the remaining proposition stated above—namely, that anæmia without mechanical injury does not cause arrest with fibrillary contractions—it should be said that the frequency of arrest after ligation is in proportion to the size of the artery ligated, and hence to the size of the area made anæmic, and is not in proportion to the injury done in the preparation of the artery. The circumflex and descendens may be prepared without injuring a single muscle-fibre, yet their ligation frequently arrests the heart, while the ligation of the arteria septi, which cannot be prepared without injuring the muscle-substance, does not arrest the heart. It is, moreover, possible to close a coronary artery without mechanical injury. Lycopodium spores mixed with defibrinated blood are injected into the arch of the aorta during the momentary closure of that vessel and are carried into the coronary arteries, the only way left open for the blood. The lycopodium spores plug up the finer branches of the coronary vessels. The coronary arteries are thus closed without the operator having touched the heart. Prompt arrest with tumultuous fibrillary contractions follows.[4] There seems, then, to be no doubt that fibrillary contractions can be brought on by *sudden* anæmia of the heart muscle.

The *gradual* interruption of the circulation in the coronary vessels—by bleeding from the carotid artery, for example—is followed by feeble incoordinated contractions not essentially different in kind from those commonly termed fibrillary contractions.[5] The manner of interruption probably explains the difference in result. In the former case, namely, ligation or other sudden closure, the supply of blood to the heart muscle is suddenly stopped while the heart continues to work against a high peripheral resistance; in the latter, the anæmia is gradual and the heart works against little or no peripheral resistance.

Recovery from Fibrillary Contractions.—Fibrillary contractions brought on by clamping the left coronary artery in the rabbit's heart are often gradually replaced by normal contractions when the clamp is removed.[6] The isolated cat's heart after showing marked fibrillary contractions during forty-five minutes has given strong regular beats for more than an hour.[7] The recovery

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[1] Porter, 1896, p. 58; see also Fenoglio and Drogoul, 1888, p. 49.
[2] Porter, 1896, p. 57; see also Rodet and Nicolas, 1896, p. 167.
[3] McWilliam, 1887, p. 298; Wooldridge, 1883, p. 532; compare Michaelis, 1894, p. 285.
[4] Porter, 1896, p. 65.　　　　　[5] Porter, 1895, p. 482.
[6] v. Bezold, 1867, pp. 263, 285.　　　　[7] Magrath and Kennedy (about to be published).

of the dog's heart has been supposed impossible.[1] McWilliam, however, has
seen a number of regular beats after the termination of fibrillary contraction.[2]
Recent results suggest that fibrillary contractions even in the highest verte-
brates may be removed by establishing an artificial circulation of defibrinated
blood through the coronary arteries.

Closure of the Coronary Veins.—Closure of all the coronary veins in
the rabbit produced fibrillary contractions after from fifteen to twenty minutes
had passed.[3] Their closure in the dog is said to be without effect [4]—a negative
result perhaps to be explained by the fact that a portion of the coronary blood
finds its way to the cavities of the heart through the venæ Thebesii.[5]

Volume of Coronary Circulation.—Bohr and Henriques,[6] taking the
average of six experiments on dogs, found that 16 cubic centimeters of blood
passed through the coronary arteries per minute for each 100 grams of heart
muscle. The quantity passing through both coronary arteries varied in dif-
ferent animals from 20 to 64 cubic centimeters per minute; the quantity
passing through the left coronary artery varied from 22.5 to 60 cubic centi-
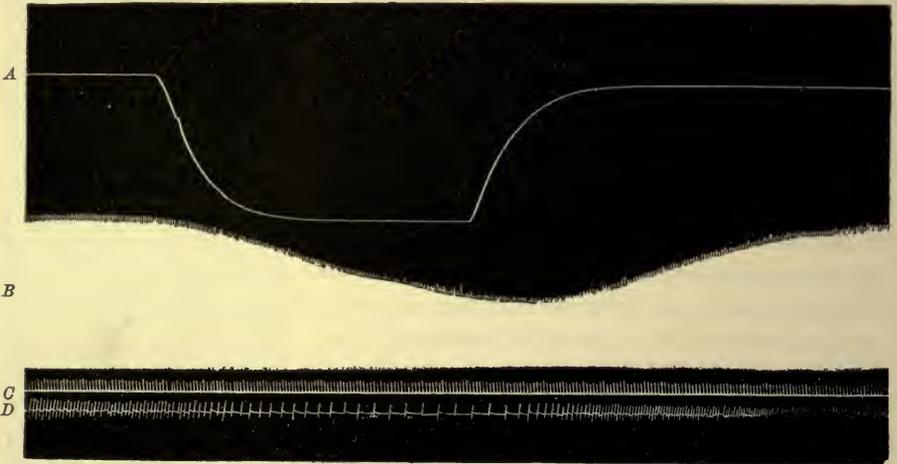
Fig. 125.—Diminution of the force of contraction of the ventricle of the isolated cat's heart in con-
sequence of diminishing the supply of blood to the cardiac muscle: *A*, blood-pressure at the root of the
aorta, recorded by a mercury manometer; *B*, intra-ventricular pressure-curve, left ventricle: the indi-
vidual beats do not appear, because of the slow speed of the smoked surface; *C*, time in seconds; *D*, the
number of drops of blood passing through the coronary arteries, each vertical mark recording one drop.
As the number of drops of blood passing through the coronary arteries diminishes, the contractions of
the left ventricle become weaker, but recover again when the former volume of the coronary circula-
tion is restored.

meters per minute. The hearts weighed from 51 to 350 grams. The method
which Bohr and Henriques found it necessary to employ placed the heart
under such abnormal conditions that their results can be regarded as only

[1] Cohnheim and v. Schulthess-Rechberg, 1881, p. 519; Tigerstedt, 1895, p. 546; and others.
[2] It is not quite clear whether McWilliam refers to fibrillary contractions produced by
closing a coronary artery or to those which follow strong faradic stimulation of the ventricle
(1887, p. 299).
[3] v. Bezold and Breymann, 1867, p. 299.   [4] Michaelis, 1894, p. 291.
[5] Gad, 1886, p. 382.   [6] Bohr and Henriques, 1895, pp. 233–236.

approximate. Porter[1] supplied the left coronary artery of the dog with blood diluted one-half with sodium chloride solution (0.6 per cent.) by means of a tube (lumen 2.75 millimeters) inserted into the aortic opening of the left coronary artery and connected with a reservoir placed 150 centimeters above the heart. In one dog, weighing 11,500 grams, 318 cubic centimeters flowed through in eight minutes. In a second dog, weighing 9500 grams, 114 cubic centimeters passed through in four minutes. In the isolated heart of the cat strong and regular contractions are made on a circulation of about 4 cubic centimeters per minute, or even less, through the coronary system. The quantity passing through the veins of Thebesius into the left auricle and ventricle is very slight.

Blood-supply and Heart-beat.—The relation between the volume of blood passing through the coronary arteries and the rate and force of the ventricular contraction has been studied by Magrath and Kennedy (1896). Variations in the volume of the coronary circulation in the isolated heart of the cat, unless very considerable, are not accompanied by changes in the rate of beat. The force of contraction, on the contrary, appears to be closely dependent on the volume of the coronary circulation (Fig. 125).

Lymphatics of the Heart.—A rich plexus of lymphatic vessels has been demonstrated in the heart. Valuable information concerning the nutrition of the heart could probably be gained by the systematic study of these vessels.

C. Solutions which Maintain the Beat of the Heart.

The beat of the heart is maintained during life by a constant supply of oxygenated blood. The blood, however, is a very complex fluid, and it can hardly be supposed that all of its constituents are of equal value to the heart. The systematic search for those constituents of the blood which are of importance to the nutrition of the heart was begun in Ludwig's laboratory in 1875 by Merunowicz.[2] The first step toward the method used by Merunowicz and his successors was taken by Cyon.[3] Cyon tied cannulas in the vena cava inferior and in one of the aortæ of the extirpated heart of the frog, and joined them by a bowed tube filled with serum. The ventricle pumped the serum through the aortic cannula and the bowed tube into the vena cava, whence it reached the ventricle again. The force of the contraction was measured by a mercury manometer which was joined by a side branch to one limb of the bowed tube.

The frog heart manometer method thus introduced by Ludwig and Cyon has undergone various modifications at the hands of Blasius and Fick,[4] Bowditch,[5] Luciani,[6] Kronecker,[7] and others. Blasius and Fick were the first to register changes in the volume of the heart by the plethysmographic method, the organ being enclosed in a vessel filled with normal saline solution and

[1] Porter, 1896, p. 64.   [2] Merunowicz, 1876, p. 132.
[3] Cyon, 1867, p. 80.   [4] Blasius, 1872, p. 9.
[5] Bowditch, 1872, p. 139.   [6] Luciani, 1873, p. 113.
[7] Kronecker, 1874, p. 174.

connected with a manometer.   This idea reappears in the Strassburg apparatus described below.

A valuable improvement was made by Kronecker, who invented a double cannula, through one side of which the "nutrient" fluid enters the ventricle while it passes out through the other (Fig. 126). The contents of the ventricle are thus continually renewed.   In 1878, Roy[1] constructed the instrument shown in Figure 127, by means of which the changes in the volume of the heart at each contraction are recorded on a moving cylinder.   A great advance was made by Williams,[2] in the invention known as "Williams's valve," which is the essential feature of the apparatus devised by this investigator and others in Schmiedeberg's laboratory at Strassburg.   The present form of this apparatus is illustrated in Figure 128.   A perfusion cannula is introduced into the ventricle through the aorta.   Through one tube of the cannula the heart is fed from a reservoir placed above it.   Through the other the heart pumps its contents into a higher reservoir or into the same reservoir.   Thus the heart is "loaded" with a column of liquid of known height and pumps against a measurable resistance.   A

FIG. 126.—The perfusion cannula of Kronecker. The ventricle is tied on the cannula at *d*, a ring being placed here to prevent the ligature from slipping. The double tube, shown in cross-section at *e*, divides into the large branch *a* and the small branch *b*. The nutrient solution enters the heart through *b* and escapes through *a*. The silver wire *c* can be connected with one pole of a battery, the cannula serving as one electrode, and the fluid surrounding the heart as the other.

FIG. 127.—Roy's apparatus: the heart is tied on a perfusion cannula and enclosed in a bell glass resting on a brass plate, *b*, the centre of which presents an opening covered by a rubber membrane. Variations in the volume of the heart cause the membrane to rise and fall. The movements of the membrane are recorded by a lever.
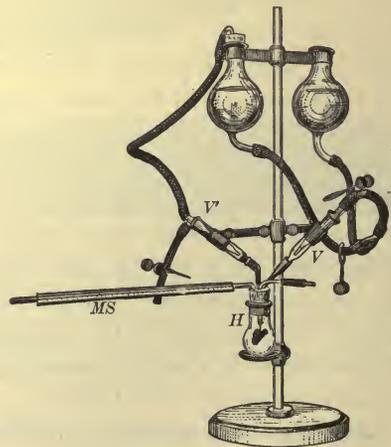
FIG. 128.—Williams's apparatus: *H*, frog's heart; *V, V'*, Williams's valves; *MS*, millimeter scale. The apparatus is arranged to feed the heart from the reservoir into which the heart is pumping.

Williams's valve in the inflow tube prevents any flow except in the direction of the heart.   A similar valve reversed in the outflow tube prevents any flow

[1] Roy, 1879, p. 453.   [2] Williams, 1881, p. 3.

except away from the heart. The ventricle is filled and emptied alternately as is the normal heart, the artificial valves replacing the heart-valves, which are often necessarily rendered useless by the introduction of the cannula and are at best less certain in their action than the artificial valve. The changes in the volume of the heart are shown by the movements of a liquid column in a horizontal tube which communicates with the bottle filled with "nutrient" fluid in which the heart is enclosed.

In the original method of Cyon the ventricle is left in connection with the auricle, the ganglion-cells of the ventricle and the neighboring portions of the auricle being kept intact. This "whole heart" preparation is to be distinguished from the "apex" preparation of Bowditch, which has also been used in studies of the effects of nutrient solutions on the heart. In Bowditch's "apex" preparation,[1] the ventricle is bound to the cannula by a thread tied at the junction of the upper and middle thirds of the ventricle. By this means the lower two-thirds of the ventricle, which contains no ganglion-cells, is cut off from any physiological connection with the base of the ventricle and a "ganglion-free apex" secured. The isolated "apex" at first stands still, but after from ten to sixty minutes[2] commences to beat again and can then be kept beating for several hours.

In the use of these various methods certain general precautions should be kept in mind. Special attention should be directed to the difficulty of removing the blood from the capillary fissures in the wall of the frog's heart.[3] A small amount of blood remaining in these passages is frequently a source of error. It should be remembered that, as Cyon[4] pointed out, a change in the nutrient solution is of itself a stimulus to the heart, increasing or diminishing the frequency of contraction and obliging the investigator to wait until the heart has become accustomed to the new solution before making an observation. The heart should, as a rule, be constantly supplied with fresh fluid, as in the natural state. The resistance against which the heart works is also a factor of importance. The water with which the solutions are made should be distilled in glass, as the minutest trace of the compounds of heavy metals in non-colloidal solutions affects the heart.[5]

Nutrient Solutions.—Cyon[6] found that the beat of the extirpated frog's heart is very dependent on the nature of the solution with which the heart is fed. Hearts supplied with normal saline solution (NaCl, 0.6 per cent.) ceased to beat much sooner than those left empty. The serum of dog's blood seemed almost poisonous. Rabbit's serum, on the contrary, postponed the exhaustion of the heart for many hours, provided the limited quantity contained in the apparatus was renewed from time to time. Serum used over and over again caused the beats to lose force after an hour or two. The renewal of the serum seemed a stimulus to the heart, causing it to contract very strongly during a half minute or more, after which the contractions became less energetic.

[1] Bowditch, 1872, p. 139.   [2] Merunowicz, 1876, p. 135.
[3] Martius and Kronecker, 1882, p. 547.   [4] Cyon, 1867, p. 89.
[5] Locke, 1895, p. 331; Naegeli, 1893, p. 12.   [6] Cyon, 1867, p. 89.

Cyon's immediate successors, Bowditch, Luciani, and Rossbach,[1] confirmed his observations. None of these investigators, however, was concerned primarily with the nutrition of the heart. The first systematic work on this subject was done, as has been said, by Merunowicz, who attempted to maintain the beat of the heart with normal saline solution containing various quantities of blood, with normal saline alone, with a watery solution of the ash of an alcholic extract of serum, and with a normal saline solution containing a minute amount of sodium carbonate. The direction taken by him has been pursued to the present day, the chief objects of study being the importance to the heart of sodium carbonate or other alkali, sodium and potassium chloride, the salts of calcium, oxygen, proteids and some other organic bodies such as dextrose, and, finally, of fluids possessing the physical characteristics of the blood. The outcome of this work we must now consider.

The value of an alkaline *reaction* has been generally recognized. Sodium carbonate is the alkali commonly preferred. The favorable influence of this salt probably does not depend on any specific action, but simply upon its alkalinity.[2] The alkali promotes the beat of the heart by neutralizing the carbon dioxide and other acids formed in the metabolism of the contracting muscle; this, however, may not be its only use.

Certain of the salts normally present in the blood are necessary to maintain the beat of the heart. *Sodium chloride* is one of these. The solution employed should contain a " physiological quantity." Such a solution is said to be " isotonic." The amount required to make a sodium chloride solution " normal " or " isotonic " for the frog is 0.6 per cent., for the mammal nearly 1 per cent. Enough of a *calcium* salt to prevent the washing out of lime from the tissues is also essential for prolonged maintenance of the contractions.[3] A heart fed with normal saline solution is before long brought to a stand; the addition of a calcium salt to the solution postpones the arrest. The character of the contraction, however, is altered by the calcium, the relaxation of the ventricle being sometimes so much delayed that the next contraction takes place before the relaxation from the previous contraction has commenced, the ventricle falling thereby into a state of persistent or " tonic " contraction. The addition of a *potassium* salt restores the normal character of the contraction,[4] calcium and potassium having an antagonistic action on the heart. The importance of calcium to the heart is said to be demonstrated by the disappearance of the spontaneous contractions of the heart which follows the precipitation of the calcium in the circulating fluid by the addition to it of an equivalent quantity of a soluble oxalate, and by the return of spontaneous contractions which is seen when the calcium is restored to the solution.[5]

The antagonistic action of calcium and the oxalates was first pointed out by Cyon.[6]

[1] Bowditch, 1872, p. 139; Luciani, 1873, p. 113; Rossbach, 1875, p. 90.

[2] Gaule, 1878, p. 294.   [3] Ringer, 1885, p. 252.

[4] Ringer, 1885, p. 247.   [5] Ringer, 1885, p. 85; compare Howell, 1894, p. 478.

[6] Cyon, 1867, p. 203; see also Sokoloff, 1881, p. 8; Ringer, 1885, p. 86; Howell and Cooke, 1893, p. 220; Howell, 1894, p. 478.

According to Ringer,[1] the substances thus far mentioned are effective in the following order: normal saline is the least effective; next is saline containing sodium bicarbonate; then saline containing tricalcium phosphate; and best of all, saline containing tricalcium phosphate together with potassium chloride. He recommends the following mixture: Sodium chloride solution 0.6 per cent., saturated with tribasic calcium phosphate, 100 cubic centimeters; solution potassium chloride 1 per cent., or acid potassium phosphate (HK_2PO_4) 1 per cent., 2 cubic centimeters.[2]

There has been considerable dispute over the part played by *oxygen* in the beat of the frog's heart. McGuire[3] and Klug[4] were of opinion that the beat is largely independent of the amount of oxygen in the circulating fluid. Yeo[5] concluded that the contracting heart uses more oxygen than the resting heart, and that the consumption of oxygen increases with the work done. Kronecker and Handler,[6] on the contrary, believe that the oxygen consumption is increased by an increase in the rate of beat, but is independent of the work done.[7] More recent observers are united on the necessity of oxygen to the working heart. Oehrwall's studies in this field are especially interesting. He finds that a volume of blood sufficient to fill the frog's ventricle will maintain contractions for hours provided the heart is surrounded by an atmosphere of oxygen. The heart is brought to a stand by lack of oxygen and may be made to beat again, even after an arrest of twenty minutes, by giving it a fresh supply. The heart fails in oxygen-hunger probably because the chemical process by which the stimulus to contraction is called forth no longer takes place, and not because of a failure in contractility, for even after long inaction a gentle touch on the pericardium will cause a vigorous contraction.

Carbon dioxide[8] is injurious to the heart when present in the circulating fluid in considerable quantities. The force of the contraction is reduced before the rate of beat. The heart poisoned with carbon dioxide often falls into irregular contractions, exhibiting at times "grouping" and the "staircase" phenomenon, a series of beats regularly increasing in strength.

Organic Substances.—An unsuccessful effort has been made to prove that only solutions containing proteids, for example blood-serum, chyle, and milk, can keep the heart active.[9] Recent observers have shown the incorrectness of this claim. The inorganic salts of serum alone suffice.[10] Locke[11] found that the addition of 0.1 per cent. of dextrose to a suitable inorganic solution kept a frog's

[1] Ringer, 1886, p. 294.

[2] Ringer, 1893, p. 128; for the action of rubidium, strontium, and cæsium on the heart see Ringer, 1884, p. 370.

[3] McGuire, 1878, p. 321.   [4] Klug, 1879, p. 478.

[5] Yeo, 1886, p. 119.   [6] Handler, 1890, p. 253.

[7] Heffter, 1892, p. 52; Albanese, 1893, p. 311; Oehrwall, 1893, pp. 42, 44.

[8] See Kronecker and Stirling, 1874, p. 200; McGuire, 1878, p. 322; Klug, 1879, p. 478; Saltet, 1882, p. 567; Kronecker and Mays, 1883, p. 263; Langendorff, 1893, p. 417; Ide, 1893, p. 492; Ringer, 1893, p. 129.

[9] Martius and Kronecker, 1882, p. 562; v. Ott, 1883, p. 26; Popoff, 1889, p. 438; Brinck, 1889, p. 472; White, 1896, p. 344; compare Stienon, 1878, p. 277, and Ringer, 1886, p. 363.

[10] Merunowicz, 1876, p. 166; Howell and Cooke, 1893, p. 204.   [11] Locke, 1895, p. 333.

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heart working under a load of 3.5 centigrams, and under an "after-load" of 3 centigrams in spontaneous activity for more than twenty-four hours. The sustaining action which dextrose appears to exercise is shared, according to him, by various other organic substances.

Physical Characteristics.—Heffter[1] and Albanese,[2] having observed that the addition of gum-arabic to the circulating fluid was of advantage, declared that the nutrient solutions should possess the viscosity of the blood. The favorable action of gum-arabic may, however, more probably be ascribed to the compounds which it contains rather than to its physical properties.[3]

Mammalian Heart.—The success attained within the past two years in the isolation of the mammalian heart opens up an hitherto unexplored region in which systematic investigation will surely bring to light facts of wide interest and value. At present, however, little is known as to the constituents of the blood which are essential to the life of the mammalian heart. An abundant supply of oxygen is certainly highly important.[4]

Blood of Various Animals.—Roy[5] gives some data as to the effect on the frog's ventricle of the blood of various animals. The blood of the various herbivora (rabbit, guinea-pig, horse, cow, calf, sheep), as well as that of the pigeon, were found to have nearly the same nutritive value in each case. That of the dog, of the cat, and more especially of the pig, while in some instances equal in effect to that from the horse or rabbit, were in other examples (from the newly killed animals) apparently almost poisonous. Cyon's early observation of the injurious action of dog's blood on the frog's ventricle has already been mentioned.

Regarding the mammalian heart, experience has shown that it is best to supply the heart with blood from the same species of animal.[7] The difficulties attending the use of blood from a different species are seen in the case of the dog's heart supplied with calf's blood. The heart dies sooner; œdema of the lungs takes place, impeding the pulmonary circulation and leading to engorgement of the right heart and paralysis of the right auricle; exudation into the pericardium often seriously interferes with the beat of the heart; and, finally, the elastic modulus of the cardiac muscle is apparently altered, permitting the heart to swell until it tightly fills the pericardium, when the proper filling of the heart is no longer possible through lack of room for diastolic expansion.

PART IV.—THE INNERVATION OF THE BLOOD-VESSELS.

About the middle of the eighteenth century more or less sagacious hypotheses concerning the contractility of the blood-vessels began to appear in medical

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[1] Heffter, 1892, p. 52.   [2] Albanese, 1893, p. 311.

[3] Howell and Cooke, 1893, p. 216; Locke, 1895, p. 333.

[4] Experiments on the artificial circulation of defibrinated blood through the coronary arteries have been performed by Martin and Applegarth, 1890, p. 275; Arnaud, 1891, p. 396; Hédon and Gilis, 1892, p. 760; Langendorff, 1895, p. 291; Porter, 1896, p. 46; Magrath and Kennedy, 1896.   [5] Roy, 1879, p. 460; compare Heffter, 1892, p. 44.

[6] Cyon, 1867, p. 89.   [7] Martin, 1883, p. 676; see also Langendorff, 1895, p. 293.

literature, but it was not until Henle demonstrated the existence of muscular elements in the middle coats of the arteries in 1840 that a secure foundation was laid for the present knowledge of the mechanism by which that contractility is made to control the distribution of the blood. More than a hundred years before, indeed, Pourfour du Petit had shown that redness of the conjunctiva was one of the consequences of the section of the cervical sympathetic, but had called the process an inflammation, in which false idea he was supported by Cruikshank and others; and Dupuy of Alfort had noted redness of the conjunctiva, increased warmth of the forehead, and sweat-drops on ears, forehead, and neck following his extirpation of the superior cervical ganglia in the horse; Brachet, also, cutting the cervical sympathetic in the dog, had gone so far as to attribute the resulting congestion to a paralysis of the blood-vessels. But these were merely clever speculations, for the anatomical basis necessary for a real knowledge of this subject was wanting as yet. Henle furnished this basis, and at the same time reached the modern point of view. "The part taken by the contractility of the heart and the blood-vessels in the circulation," said Henle, "can be expressed in two words: the movement of the blood depends on the heart, but its distribution depends on the vessels." Nor did Henle stop here. It was now known that the vessels possessed contractile walls; it was known further that these walls contracted when mechanically stimulated; for example, by scraping them with the point of a scalpel; and various observers had traced sympathetic nerves from the greater vessels to the lesser until lost in their finest ramifications. It was therefore easy to construct a reasonable hypothesis of the control of the blood-vessels by the nerves. Henle declared that the vessels contract because their nerves are stimulated, either directly, or reflexly through the agency of a sensory apparatus. The ground was thus prepared for the physiological demonstration of the existence of "vaso-motor" nerves, as Stilling began to call them. Four names are associated with this great achievement—Schiff, Bernard, Brown-Séquard, and Waller,[1] each of whom worked independently of the others. Foremost among them is Claude Bernard, though not the first in point of time, for it was he who put the new doctrine on a firm basis. In his first publication Bernard[2] stated that section of the cervical sympathetic, or removal of the superior cervical ganglion, in the rabbit, causes a more active circulation on the corresponding side of the face together with an increase in its temperature. The greater blood-supply manifests itself in the increased redness of the skin, particularly noticeable in the skin of the ear. The elevation of temperature may be easily felt by the hand. A thermometer placed in the nostril or in the ear of the operated side shows a rise of from 4° to 6° C. The elevation of temperature may persist for several months. Similar results are obtained in the horse and the dog.

The following year Brown-Séquard[3] announced that "if galvanism is applied

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[1] Waller, 1853, p. 378. The literature of vaso-motor nerves is so large that only works of the past fifteen years can be cited, except in a few important instances.

[2] Bernard, 1851, p. 163.   [3] Brown-Séquard, 1852, p. 490.

to the superior portion of the sympathetic after it has been cut in the neck, the dilated vessels of the face and of the ear after a certain time begin to contract; their contraction increases slowly, but at last it is evident that they resume their normal condition, if they are not even smaller. Then the temperature diminishes in the face and the ear, and becomes in the palsied side the same as in the sound side. When the galvanic current ceases to act, the vessels begin to dilate again, and all the phenomena discovered by Dr. Bernard reappear." Brown-Séquard concludes that "the only direct effect of the section of the cervical part of the sympathetic is the paralysis, and consequently the dilatation, of the blood-vessels. Another evident conclusion is that the cervical sympathetic sends motor fibres to many of the blood-vessels of the head."

While Brown-Séquard was making these important investigations in America, Bernard, in Paris, quite unaware of Brown-Séquard's labors, was reaching the same result. The existence of nerve-fibres the stimulation of which causes constriction of the blood-vessels to which they are distributed was thus established.

A considerable addition to this knowledge was presently made by Schiff,[1] who pointed out in 1856 that certain vaso-motor nerves take origin from the spinal cord. The destruction of certain parts of the spinal cord causes the same vascular dilatation and rise of temperature that follows the section of the vaso-motor nerves outside the spinal cord.

At this time Schiff also offered evidence of vaso-dilator nerves. When the left cervical sympathetic is cut in a dog, and the animal is kept in his kennel, the left ear will always be found to be 5° to 9° warmer than the right. If the dog is now taken out for a run in the warm sunshine, and allowed to heat himself until he begins to pant with outstretched tongue, the temperature of both ears will be found to have increased. The right ear is now, however, the warmer of the two, being from 1° to 5° warmer than the left. The blood-vessels of the right ear are, moreover, now fuller than those of the left. When the animal is quiet again the former condition returns, the redness and warmth in the right becoming again less than in the left ear. The increase of the redness and warmth of the right ear over the left, in which the vaso-constrictor nerves were paralyzed, must be the result of a dilatation of the vessels of the right ear by some nervous mechanism. For if the dilatation of the vessels was merely passive, the vessels in the right ear could not dilate to a greater degree than those in the left ear which had been left in a passive state by the section of their nerves. This experiment, however, is by no means conclusive.

The existence of vaso-dilator fibres was placed beyond doubt by the following experiment of Bernard [2] on the chorda tympani nerve, new facts regarding the vaso-constrictor nerves being also secured. Bernard exposed the submaxillary gland of a digesting dog, removed the digastric muscle, isolated the nerves going to the gland, introduced a tube into the duct, and, finally, sought

[1] Schiff, 1856, p. 69 ; 1859, p. 153.
[2] Bernard, 1858, p. 241; see also pp. 649 to 658.

out and opened the submaxillary vein. The blood contained in the vein was dark. The nerve-branch coming to the gland from the sympathetic was now ligated, whereupon the venous blood from the gland grew red and flowed more abundantly; no saliva was excreted. The sympathetic nerve was now stimulated between the ligature and the gland. At this the blood in the vein became dark again, flowed in less abundance and finally stopped entirely. On allowing the animal to rest the venous blood grew red once more. The chorda tympani nerve, coming from the lingual nerve, was now ligated, and the end in connection with the gland stimulated. Then almost at once saliva streamed into the duct, and large quantities of bright scarlet blood flowed from the vein in jets, synchronous with the pulse.

This experiment may be said to close the earlier history of the vaso-motor nerves.[1] It was now established beyond question that the size of the blood-vessels, and thus the quantity of blood carried by them to different parts of the body, is controlled by nerves which when stimulated either narrow the blood vessels (vaso-constrictor nerves) and thus diminish the quantity of blood that flows through them, or dilate the vessels (vaso-dilator nerves) and increase the flow. The section of vaso-constrictor nerves, for example those found in the cervical sympathetic, causes the vessels previously constricted by them to dilate. The section of a vaso-dilator nerve, for example the chorda tympani, running from the lingual nerve to the submaxillary gland, does not, however, cause the constriction of the vessels to which it is distributed. And finally, it was now determined that vaso-motor fibres are found in the sympathetic system as well as in the spinal cord and the cerebro-spinal nerves.

It remained for a later day to show that vaso-motor nerves are present in the veins as well as in the arteries. Mall [2] has found that when the aorta is compressed below the left subclavian artery, the portal vein receives no more blood from the arteries of the intestine, yet remains for a time moderately full, because it cannot immediately empty its contents through the portal capillaries of the liver against the resistance which they offer. If the peripheral end of the cut splanchnic nerve is now stimulated, the portal vein contracts visibly and may be almost wholly emptied. Thompson [3] has extended the discovery of Mall to the superficial veins of the extremities. He finds that the stimulation of the peripheral end of the cut sciatic nerve, the crural artery being tied, causes the constriction of the superficial veins of the hind limb. The contraction begins soon after the commencement of the stimulation, and usually goes so far as to obliterate the lumen of the vein. Often the contraction begins nearer the proximal portion of the vein and advances toward the periphery. More commonly, however, it is limited to band-like constrictions between which the vein is filled with blood. After stimulation ceases the constrictions gradually disappear. A second and third stimulation produce

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[1] Further information regarding the history of this subject is given by Vulpian, *Leçons sur l'appareil vaso-moteur*, Paris, 1875; Longet, *Traité de physiologie*, Paris, 1869, t. ii. p. 199; and Schiff, *Untersuchungen zur Physiologie des Nervensystems*, Frankfort-am-Main, 1855, Bd. i. p. 124.

[2] Mall, 1890, p. 57; 1892, p. 409.   [3] Thompson, 1893, p. 104.

much less constriction. The superficial veins of the rabbit's abdomen are constricted by the stimulation of the cervical spinal cord at the second vertebra.

The observations of Bernard and his contemporaries led to a very great number of researches on the general properties and the distribution of the vaso-motor nerves, in the course of which a variety of ingenious methods of observation have been devised.

Methods of Observation.—One fruitful method of research has been already incidentally mentioned, namely, the direct inspection of the vessel, or region, the vaso-motor nerves of which are being studied.

A second method consists in accurately measuring the outflow from the vein. If the blood-vessels of the area drained by the vein are constricted by the stimulation of a vaso-motor nerve, the quantity escaping from the vein in a given period previous to constriction will be greater than that escaping in an equal period during constriction. This well-known method is especially available where an artificial circulation is kept up through the organ studied, as the blood drained from the vein does not then weaken the animal and thus disturb the accuracy of the observations.[1]

A third method is founded on the principle in hydraulics that the lateral pressure at any point in a tube through which a liquid flows depends, other things being equal, on the resistance to be overcome below the point at which the pressure is measured. In the animal body the resistance to be overcome by the blood-stream varies with the state of contraction of the smaller vessels, and thus the variations in the lateral pressure of a given artery may, under certain restrictions, be used to determine variations in the size of the smaller vessels distal to the artery. The restrictions are, that the variations in the lateral pressure in the artery are indicative of changes in the size of the distal vessels only when the general blood-pressure remains unaltered, or alters in a direction opposite to the change in the artery investigated.[2] An example will make this plain. Dastre and Morat,[3] in order to demonstrate the presence of vaso-motor fibres for the hind limb in the sciatic nerve, connected a manometer with the central end of the left femoral artery, and a second manometer with the peripheral end of the right femoral artery, distal to the origin of the profunda femoris. The anastomoses between the principal branches of the femoral artery are so numerous and so large that the circulation in the limb can be maintained by the profunda femoris alone. Dastre and Morat could therefore compare the general blood-pressure with the blood-pressure in the right hind limb. On stimulating the peripheral end of the right sciatic nerve, the blood-pressure rose in the arteries of the limb, but remained stationary in the arteries of the trunk, connected with the first manometer through the central end of the left femoral artery. The rise of blood-pressure in the operated limb, while the blood-pressure in the rest of the body remained unchanged, proved that the vessels in the operated limb were constricted.

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[1] Cavazzani and Manca, 1895, p. 33. [2] Hürthle, 1889, p. 563.

[3] Dastre and Morat, 1883, p. 556.

Many investigators have studied vaso-motor phenomena by means of the plethysmograph, an apparatus invented by Mosso for recording the changes in the volume of the extremities. The member, the vaso-motor nerves of which are to be studied, is placed within a cylinder filled with water, from which a tube leads to a recording tambour.[1] An increase in the volume of the member, such as would be brought about by the expansion of its vessels, causes a corresponding volume of water to enter the tambour tube, thus raising the pressure in the tambour and forcing its lever to rise. A constriction of the vessels, on the contrary, causes the recording lever to fall.

In addition to these general methods, special devices have been employed in the researches into the vaso-motor nerves of the brain.

In considering the observations made with these various methods it will be advisable to begin with the differences between the two kinds of vaso-motor nerves.

Differences between Vaso-constrictor and Vaso-dilator Nerves.—The differences between vaso-constrictor and vaso-dilator nerves are particularly interesting for the reason that both vaso-constrictor and vaso-dilator fibres are often found in one and the same anatomical nerve. The sciatic nerve is a good example of this. By taking advantage of these differences the investigator may determine whether one or both kinds of fibres are present in any anatomical nerve; whereas, without this knowledge, the effects produced by the stimulation of the one might be wholly masked by the effects produced by the stimulation of the other.

The vaso-constrictors are less easily excited than the vaso-dilators. The simultaneous and equal stimulation of the dilator and constrictor nerves going to the submaxillary gland causes vaso-constriction, dilatation appearing after the stimulation ceases, for the after-effect of excitation is of shorter duration with the constrictors than with the dilators.[2] Warming increases and cooling diminishes the excitability of the vaso-constrictors to a greater degree than is the case with the vaso-dilators. Thus if the hind limb of an animal be warmed, the stimulation of the sciatic nerve will cause vaso-constriction; while if it be cooled the same stimulation will cause vaso-dilatation.[3] Vaso-constrictors are more sensitive to rapidly repeated induction shocks (tetanization) and less sensitive to single induction shocks than are vaso-dilators. Thus if the sciatic nerve is stimulated with induction shocks of the same strength, it will be found that a rapid repetition of the stimuli will give vaso-constriction, while with single shocks at intervals of five seconds vaso-dilatation is the result.[4] Vaso-constrictors degenerate more rapidly than vaso-dilators after separation from their cells of origin. The stimulation of the peripheral end of the frog's sciatic nerve immediately after section causes constriction. Several days later the same stimulation causes vaso-dilatation, the constrictor nerves having already

[1] An improved method of recording is given by Bowditch and Warren, 1886, p. 420.
[2] Anrep and Cybulski, 1884.
[3] Lépine, 1876, p. 26; Howell, Budgett, and Leonard, 1894, p. 306.
[4] Ostroumoff, 1876, p. 232; Bowditch and Warren, 1886, p. 436; Bradford, 1889, p. 390.

degenerated [1] (see Fig. 129, *B*). The maximum effect of stimulation is more quickly reached with the vaso-constrictor than with the vaso-dilator nerves. There is also a difference in the latent period, or interval between stimulation
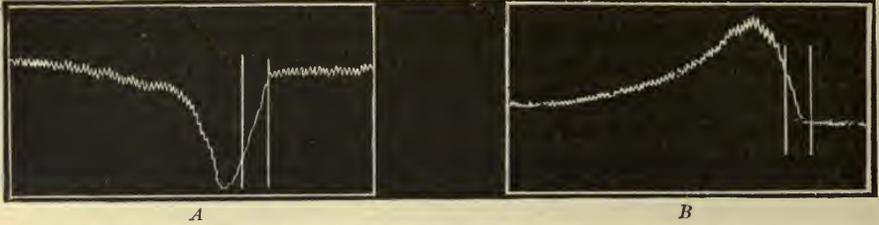
FIG. 129.—Curves obtained by enclosing the hind limb of a cat in the plethysmograph and stimulating the peripheral end of the cut sciatic nerve (Bowditch and Warren, 1886, p. 447). The curves read from right to left. In each case the vertical lines show the duration of the stimulus—namely, fifteen induction shocks per second during twenty seconds. Curve *A* shows the contraction of the vessels produced by the excitation of the freshly-divided nerve; curve *B*, the dilatation produced by an equal excitation of the nerve of the opposite side four days after section, the vaso-constrictor nerves having degenerated more rapidly than the vaso-dilators.

and response. Bowditch and Warren [2] have found the latent period of the vaso-constrictor fibres in the sciatic to be about 1.5 seconds, while that of the vaso-dilators is 3.5 seconds. Finally, the two sorts of nerves have been said to differ in the manner in which they are distributed. The vaso-constrictor nerves leave the cord as medullated fibres, enter the sympathetic chain of ganglia and end in terminal branches probably in contact with a sympathetic ganglion-cell. The constrictor impulse is forwarded to the vessel by a process of this cell, either directly or by means of still other sympathetic ganglion-cells. The vaso-dilator fibre, on the contrary, was thought to run directly from the cord to the blood-vessel; [3] but the latest investigations make it probable that all spinal vaso-motor fibres end in sympathetic ganglia. [4]

Origin and Course.—The vaso-motor nerves the general properties of which have just been studied are axis-cylinder processes of sympathetic ganglion-cells. They follow, for a time at least, the course of the corresponding spinal nerve. According to Langley, [5] they do not differ from the pilo-motor and secretory nerves except in the nature of the structure in which they terminate. They are not interrupted by other nerve-cells on their course. The action of the sympathetic vaso-motor cells is influenced by the vaso-motor cells of the spinal cord and bulb. These are probably small cells situated at various levels in the anterior horn and lateral gray substance. [6] Their axis-cylinder processes leave the cerebro-spinal axis by the anterior roots [7] of

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[1] Ostroumoff, 1876, p. 228; Bowditch and Warren, 1886, p. 444.

[2] Bowditch and Warren, 1886, p. 440.   [3] Kölliker, 1894, p. 2.

[4] Langley, 1895, p. 314.   [5] Langley, 1895, p. 314.   [6] Kölliker, 1894, p. 6 (reprint).

[7] Budge, 1853, p. 378. Some investigators hold that vaso-motor nerves leave the cord in the posterior as well as the anterior roots. Stricker [1] observed that excitation of the peripheral end of the posterior roots of the sciatic nerve is followed by a rise of temperature in the hind limb. This was denied by Kühlwetter. [2] Bonuzzi [3] and Gärtner [4] agreed with Stricker. Morat [5] found

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[1] Stricker, 1877, p. 279.   [2] Kühlwetter, 1885, p. 40.   [3] Bonuzzi, 1885, p. 473.   [4] Gärtner, 1889, p. 980.

[5] Morat, 1892, pp. 1499, 694; see also Bradford, 1889, p. 363, and Morat, 1890, p. 473.

certain spinal and by certain cranial nerves, and enter sympathetic ganglia, where they end in terminal twigs probably in contact with the sympathetic vaso-motor cells. The vaso-motor cells lying at various levels in the cerebro-spinal axis are in turn largely controlled by an association of cells situated in the bulb and termed the vaso-motor centre. The neuraxons (axis-cylinder processes) of the cells composing this "centre" pass in part to the nuclei of certain cranial nerves and in part down the lateral columns[1] of the cord, to end in contact with the spinal vaso-motor cells. The vaso-motor apparatus consists, then, of three classes of nerve-cells.[2] The cell-bodies of the first class lie in sympathetic ganglia, their neuraxons passing directly to the smooth muscles in the walls of the vessels; the second are situated at different levels in the cerebro-spinal axis, their neuraxons passing thence to the sympathetic ganglia by way of the spinal and cranial nerves; and the third are placed in the bulb and control the second through intraspinal and intracranial paths. The nerve-cell of the first class lies wholly without the cerebro-spinal axis, the third wholly within it, while the second is partly within and partly without, and binds together the remaining two.

The evidence for the existence of these vaso-motor nerve-cells must now be considered. We shall begin with those of the third class, constituting the so-called bulbar vaso-motor centre.

Bulbar Vaso-motor Centre.—The section of the spinal cord near its junction with the bulb is followed by the general dilatation of the blood-vessels of the trunk and limbs.[3] The dilated vessels are again constricted when the severed fibres in the spinal cord are artificially stimulated. Hence the section caused the dilatation by interrupting the vaso-constrictor impulses passing from the bulb to parts below. The position of the bulbar vaso-constrictor centre has been determined by Owsjannikow and Dittmar. The former observer[4] divided the bulb transversely at various levels. When the section fell immediately caudal to the corpora quadrigemina, only a slight temporary rise in blood-pressure was observed. When, however, the section fell a millimeter or two nearer the cord, a considerable and permanent fall in the blood-pressure was noted. Further lowering was seen as the sections were carried still farther toward the spinal cord, until at length, about four millimeters from the corpora quadrigemina, no further fall took place. The area from which the vaso-constrictor nerves receive a constant excitation extends, therefore, in the rabbit, over about three millimeters of the bulb not far from the corpora quadrigemina. Two years after this investigation Dittmar added to the observations of Owsjannikow the fact that the vaso-con-

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in a curarized dog that excitation of the peripheral end of certain lumbo-sacral posterior roots causes primary vascular dilatation in the pulp of the hind paw corresponding to the nerves stimulated. The fibres in question do not degenerate after section of the root containing them, and are therefore not of spinal origin.

[1] Compare Nicolaides, 1882, p. 28; Helweg, 1886, quoted by Tigerstedt, 1893, p. 536.

[2] By "nerve-cells" is meant the cell-body with all its processes, namely, the neuraxon, or axis-cylinder process, and the dendrites, or protoplasma processes.

[3] Waller, 1853, p. 381.   [4] Owsjannikow, 1871, p. 25.

strictor centre is bilateral, lying in the anterior part of the lateral columns on both sides of the median line.[1]   At this site is found a group of ganglion-cells known as the antero-lateral nucleus of Clarke. It is possible, though far from certain, that these are the cells of the vaso-constrictor centre.

The vaso-constrictor centre in the bulb is always in a state of action, or "tonic" excitation, as is shown by the dilatation of the vessels when deprived of their constrictor impulses through the section of the spinal cord.

It is not definitely known whether a vaso-dilator centre is present in the bulb.

Spinal Centres.—A complete demonstration of the existence of vaso-motor centres in the spinal cord, first suggested by Marshall Hall, was made by Goltz and Freusberg[2] in their experiments on dogs which had been kept alive after the division of the spinal cord at the junction of the dorsal and the lumbar regions. This operation cuts off both sensory and motor communication between the parts lying above and below the plane of section, and divides the animal physiologically into a fore dog and a hind dog, to use the author's expression. The investigator can now explore the lumbar cord unvexed by cerebral impulses. A great number of motor reflexes formerly thought to have their centres exclusively in the brain are by this means found to take place in the absence of the brain.[3]   That vaso-motor reflexes were among them was discovered by accident. It was noticed that the mechanical stimulation of the skin of the abdomen and penis while the animal was being washed provoked erection, which, as Eckhard[4] had discovered some years before, is a reflex action due to the dilatation of the arteries of the penis through impulses conveyed by the nervi erigentes. Pressure on the bladder, or the walls of the rectum, also had this effect. After the destruction of the lumbar cord this reflex was no longer possible. The vessels of the hind limb are also connected with vaso-motor cells in the lumbar cord. Soon after the section of the cord in the dorsal region the hind paws are observed to be warmer than the fore paws, and the arteries of the hind limb are seen to beat more strongly. This is the result of cutting off the vaso-constrictor impulses from the bulbar centre to the vessels in question. If the animal survives a considerable time the hind paws will be observed to grow cooler from day to day until they are again no warmer than the fore paws. Destruction of the lumbar cord now causes the temperature of the hind limbs to rise again.

The conclusion drawn from these observations is that vaso-motor cells are present in the spinal cord. It is probable that they are normally subordinated to the bulbar nerve-cells and require a certain time after separation from the bulb in order to develop their previously rudimentary powers. Hence the

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[1] Dittmar, 1873, pp. 110, 114. Other literature: Schiff, 1855, p. 198; Heidenhain, 1870, 510; Latschenberger and Deahna, 1876, p. 183; Stricker, 1886, p. 13.

[2] Goltz and Freusberg, 1874, p. 463. Other literature: Smirnow, 1886, p. 145; Ustimowitsch, 1887, p. 187; Thayer and Pal, 1888, p. 29; Konow and Stenbeck, 1889, p. 409.

[3] Later experiments by Goltz and Ewald, showing the degree of independence of the spinal cord possessed by sympathetic vaso-motor neurons will presently be cited.

[4] Eckhard, 1863, p. 144.

interval of many days between the section and the return of arterial tone in areas distal to the section. It has been suggested that during this period the power of the spinal nerve-cell is inhibited by impulses proceeding from the cut surface of the cord,[1] but this long inhibition is questionable in view of the fact that transverse section of the cord in rabbits and dogs does not inhibit the phrenic nuclei.[2]

The spinal nerve-cell takes part in vaso-motor reflexes. Thus the stimulation of the central end of the brachial nerves after section of the spinal cord at the third vertebra causes a dilatation of the vessels of the fore limb.[3] The stimulation of the central end of the sciatic nerve after the division of the spinal cord causes a general rise of blood-pressure indicating the constriction of many vessels. The sensory stimulation of one hind limb may cause reflexly a narrowing of the vessels in the other, after the spinal cord is severed in the mid-thoracic region.[4] In asphyxia, after the separation of the cord from the brain, vascular constriction is produced reflexly through the spinal centres.[5] This constriction is not observed if the cord is previously destroyed.[6] Goltz and Ewald [7] find that the tonic constriction of the vessels of the hind limbs returns after the extirpation of the lower part of the spinal cord.

Sympathetic Vaso-motor Centres.—Gley [8] finds that after the destruction of both bulbar and spinal centres some degree of vascular tone is still maintained. The extraordinary experiments of Goltz and Ewald [9] place this fact beyond question. These physiologists remove the lower part of the spinal cord completely, taking away 80 millimeters or more. For a few days after the operation the hind limbs are hot and red, from dilatation of their bloodvessels. Soon, however, the hind limbs become as cool, and sometimes even cooler, than the fore limbs, their arterial tonus being re-established and maintained without the help of the spinal cord.

The sympathetic ganglia are probably also centres of reflex vaso-motor action. The fact that these ganglia act as centres for other motor reflexes would itself suggest this possibility. A direct proof of the vaso-motor reflex [10] function of the first thoracic ganglion has been given recently by François Franck.[11] The two branches composing the annulus of Vieussens contain both afferent and efferent fibres. If one of the branches is cut, and the end in connection with the first thoracic ganglion is stimulated, the ganglion having been separated from the spinal cord by the section of the communicating branches, a constriction of the vessels of the ear, the submaxillary gland, and the nasal mucous membrane may be observed.

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[1] Goltz and Ewald, 1896, p. 397. [2] Porter, 1895, p. 459.

[3] Smirnow, 1886, p. 147 ; compare Thayer and Pal, 1888, p. 29.

[4] Vulpian, 1875, p. 290. [5] Kowalewsky and Adamük, 1868, p. 582.

[6] Konow and Stenbeck, 1889, p. 409. [7] Goltz and Ewald, 1891, p. 496 ; 1896, p. 388.

[8] Gley, 1894, p. 704. [9] Goltz and Ewald, 1896, p. 389.

[10] See Wertheimer, 1890, p. 519 ; Navrocki and Skabitschewsky, 1891, p. 156 ; Langley and Anderson, 1893, p. 417 ; Franck, 1894, p. 717 ; compare Mosso and Pellacani, 1882, p. 300 ; also Goltz and Ewald, 1896, p. 391.

[11] Franck, 1894, p. 721 ; see also Roschansky, 1889, p. 162.

This evidence, together with the probability that the neuraxons of all the spinal vaso-motor cells end in sympathetic ganglia,[1] makes it fairly credible that the sympathetic vaso-motor nerve-cell possesses central functions.

There has been much discussion over the meaning of the rhythmic contractions observed in certain blood-vessels apparently independent of the central nervous system.[2]   The median artery of the rabbit's ear, the arteria saphena in the same animal, and the vessels in the frog's web and frog's mesentery, slowly contract and relax.   This rhythmic contraction is easily seen in the ear of a white rabbit.   The movements are possibly of purely muscular origin, but are more probably the result of periodical discharges by vaso-motor nerve-cells.

Rhythmical variations in the tonus of the vaso-constrictor centres are often held to explain the oscillations seen in the blood-pressure curve after the influence of thoracic aspiration has been eliminated by opening the chest and cutting the vagus nerves.   These oscillations are of two sorts.   In the one, the blood-pressure sinks with every inspiration and rises with every expiration, though the rise and fall are not precisely synchronous with the respiratory movements; in the other, the so-called Traube-Hering waves, the oscillations embrace several respirations.   It has also been suggested that these phenomena are due to periodical changes in the respiratory centre affecting the vaso-constrictor centre by "irradiation."[3]

Vaso-motor Reflexes.—The vaso-motor nerves can be excited reflexly by afferent impulses conveyed either from the blood-vessels themselves or from the end-organs of sensory nerves in general.   The existence of reflexes from the blood-vessels may be shown by Heger's experiment.   Heger[4] observed a rise of general blood-pressure with a subsequent fall, and at times a primary fall, after the injection of nitrate of silver into the peripheral end of the crural artery of a rabbit.   The limb, with the exception of the sciatic nerve, was severed from the trunk.   The quantity injected was so small that it probably was decomposed before passing the capillaries or escaping from the blood-vessels.   Thus the effect exerted by the nitrate of silver on the general blood-pressure was probably caused by afferent impulses set up in the blood-vessels themselves and transmitted through the sciatic nerve to the vaso-motor centres.   Vaso-motor reflexes are, however, much more commonly produced by the stimulation of sensory nerves other than those present in the blood-vessels.

The reflex constriction or dilatation[5] appears usually in the vascular area

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[1] See the statement of Langley's results with the nicotin method on page 500.

[2] Literature: Schiff, 1854, p. 508; Mosso, 1880, p. 66; Pye-Smith, 1887, p. 48; Fredericq, 1887, p. 351; Konow and Stenbeck, 1889, p. 406.   Discussion of the active dilatation of the blood-vessels has been recently revived by Piotrowski, 1892, p. 701; Grünhagen, 1892, p. 829; Franck, 1893, p. 729; Biedl, 1894; Stefani, 1894, pp. 237, 245; Lui, 1894, p. 416; Goltz and Ewald, 1896, p. 396.

[3] Compare Fredericq, 1882, p. 71; Knoll, 1885, p. 439.   [4] Heger, 1887, p. 197.

[5] For a study of reflex constriction and dilatation produced by stimulating the skin see Maragliano and Lusona, 1889, p. 246; compare Hegglin, 1894, p. 25.

from which the afferent impulses arise. For example, the stimulation of the central end of the posterior auricular nerve in the rabbit causes a passing constriction followed by dilatation, or a primary dilatation often followed by constriction of the vessels in the ear. The stimulation of the nervi erigentes causes dilatation of the vessels of the penis.[1] Gaskell[2] found that the vessels of the mylo-hyoid muscle widened on stimulating the mucous membrane at the entrance of the glottis.

The vascular reflex[3] may appear in a part associated in function with the sensory surface stimulated. Thus the stimulation of the tongue causes dilatation of the blood-vessels in the submaxillary gland.[4] Frequently the vascular reflex is seen on both sides of the body. The stimulation of the mucous membrane on one side of the nose may cause vascular dilatation in the whole head;[5] the effect in this case is usually more marked on the side stimulated. The vessels of one hand contract when the other hand is put in cold water.[6] Sometimes distant and apparently unrelated parts are affected. Vulpian[7] noticed that the stimulation of the central end of the sciatic caused the vessels of the tongue to contract.

The vascular changes produced reflexly in the splanchnic area are of especial importance because of the great number of vessels innervated through these nerves and the great changes in the blood-pressure that can follow dilatation or constriction on so large a scale.

There is in some degree an inverse *relation between the vessels of the skin and deeper parts* on reflex stimulation of the vaso-motor centres. The superficial vessels are often dilated while those of deeper parts are constricted.[8] Thus the stimulation of the central end of the sciatic nerve may cause a dilatation of the vessels of the lips, hand in hand with a rise in general blood-pressure.[9] Exposing a loop of intestine dilates the intestinal vessels in the rabbit, but constricts those of the ear.[10] In asphyxia, the superficial vessels of the ear, face, and extremities dilate, while the vessels of the intestine, spleen, kidneys and uterus are constricted.[11]

Relation of Cerebrum to Vaso-motor Centres.—A rise of general blood-pressure has been produced by the stimulation of different regions of the cortex and of various other parts of the brain; for example, the crura cerebri and corpora quadrigemina. Vaso-dilatation has also been observed. The motor area of the cortex especially seems closely connected with the bulbar vaso-motor centres. There is, however, no conclusive evidence that special vaso-

[1] Eckhard, 1863, p. 144. [2] Gaskell, 1877, p. 742.
[3] The general arrangement of the matter in this paragraph is that given by Tigerstedt, 1893, p. 519. [4] Bernard, 1858, p. 656. [5] Franck, 1889, p. 555.
[6] Brown-Séquard and Tholozan, 1858, p. 500; compare Teissier and Kaufmann, 1881, p. 1302; and Ranvier, 1892, p. 629.
[7] Vulpian, 1875, p. 238; compare Sergejew, 1894, p. 162.
[8] Grützner and Heidenhain, 1878, p. 20; Dastre and Morat, 1884, p. 329; Wertheimer, 1893, p. 595; 1894, p. 724; Franck, 1896, p. 502; compare Bayliss and Bradford, 1894, p. 17.
[9] Wertheimer, 1891, p. 548; compare Isergin, 1894, p. 448.
[10] Pawlow, 1878, p. 268. [11] Heidenhain, 1872, p. 100.

motor centres exist in the brain aside from the bulbar centres already described. At present the safer view is that the changes in blood-pressure called forth by the stimulation of various parts of the brain are reflex actions, the afferent impulse starting in the brain as it might in any other tissue peripheral to the vaso-motor centres.[1]

Pressor and Depressor Fibres.—The stimulation of the same afferent nerve sometimes causes reflex dilation of the vessels of a part, instead of the more usual reflex constriction. Two explanations of this fact have been suggested. The first assumes that the condition of the vaso-motor centre varies in such a way that the same stimuli might produce contrary effects, depending on the relation between the time of stimulation and the condition of the centre. The second assumes the existence of special reflex constrictor or "pressor" fibres, and reflex dilator or "depressor" fibres. The existence of at least one depressor nerve is beyond question, namely the cardiac depressor nerve, which it will be remembered runs from the heart to the bulb and when stimulated causes a dilatation of the splanchnic and other vessels reflexly through the bulbar vaso-motor centre. Evidence of other reflex vaso-dilator nerves and of reflex vaso-constrictor fibres as well has been offered by Latschenberger and Deahna,[2] Howell,[3] and others. Howell, for example, has found that if a part of the sciatic nerve is cooled to near 0° C. and the central end stimulated peripherally to this part, the blood-pressure falls, instead of rising, as it does when the nerve is stimulated without previous cooling. Howell's experiments have been recently extended by Hunt,[4] who finds that the stimulation of the sciatic during its regeneration after section gives at first vaso-dilatation only, but when regeneration has progressed still further, vaso-constriction is secured. These results point to the existence of both pressor and depressor fibres, the latter being the first to regenerate after section. A reflex fall in blood-pressure is also produced by stimulating various mixed nerves with weak currents[5] and by the mechanical stimulation of the nerve-endings in muscle. The fall is more readily obtained when the animal is under ether, chloroform, or chloral, less readily under curare.

Topography.—We pass now to the vaso-motor nerves of various regions.

Brain.[6]—The study of the innervation of the intracranial vessels is rendered exceptionally difficult by the fact that the brain and its blood-vessels are placed in a closed cavity surrounded by walls of unyielding bone. The fundamental difference created by this arrangement between the vascular phenomena

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[1] Literature: Dogiel, 1880, p. 420; Stricker, 1886, p. 9; Bechterew and Mislawsky, 1886, p. 193; Franck, 1887, p. 162.

[2] Latschenberger and Deahna, 1876, p. 165.

[3] Howell, Budgett, and Leonard, 1894, p. 310. Other literature: Belfield, 1882, p. 298; Knoll, 1885, p. 447, 1889, p. 249; Kleen, 1887, p. 247; Bayliss, 1893, p. 317; Bradford and Dean, 1894, p. 67; Hunt, 1895, p. 381.

[4] Hunt, 1895, p. 381.

[5] See also Knoll, 1885, p. 451.

[6] Literature: Mosso, 1880, p. 1–127; Franck, 1887, p. 199; Gaertner and Wagner, 1887, p. 602; Corin, 1888, p. 185; Hürthle, 1889, p. 561; Roy and Sherrington, 1890, p. 85; Cavazzani, 1891, p. 23; 1893, pp. 54, 214; Bayliss and Hill, 1895, p. 334; Gulland, 1895, p. 361.

of the brain and those of other organs was recognized in part at least by the younger Monro as long ago as 1783. Monro declared that the quantity of blood within the cranium is almost invariable, "for, being enclosed in a case of bone, the blood must be continually flowing out of the veins that room may be given to the blood which is entering by the arteries,—as the substance of the brain, like that of the other solids of our body, is nearly incompressible." Further differences between the circulation in the brain and in other organs are introduced by the presence of the cerebro-spinal fluid in the ventricles and in the arachnoidal spaces at the base of the brain. This fluid may pass out into the spinal canal and thus leave room for an increase in the amount of blood in the cranium. Finally, a rise of pressure in the arteries too great to be compensated by the outflow of cerebro-spinal fluid may lead to compression of the venous sinuses and a decided change in the relative distribution of the blood in the arteries, capillaries and veins—conditions which are not present in extracranial tissues. It is evident, therefore, that the methods employed in the search for vaso-motor nerves within the cranium must take into account many sources of error that are absent in vaso-motor studies of other regions. It is, indeed, probable that incompleteness of method will go far toward explaining the disagreement of authors as to the presence of vaso-motor nerves in the brain. According to Bayliss and Hill,[1] the most recent investigators of this subject, it is necessary to record simultaneously the arterial pressure, the general venous pressure, the intracranial pressure and the cerebral venous pressure, the cranium as in the normal condition being kept a closed cavity. In their experiments, "a cannula was placed in the central end of the carotid artery. A second long cannula was passed down the external jugular vein, and on the same side, into the right auricle. The torcular Herophili was trephined, and a third cannula, this time of brass, was screwed into the hole thus made." The intracranial pressure was recorded by a cannula connected through another trephine-hole with the subdural space.

Bayliss and Hill could find no evidence of the existence of cerebral vaso-motor nerves. The cerebral circulation, according to them, passively follows the changes in the general arterial and venous pressure. Gulland[2] has examined the cerebral vessels by the Golgi, Ehrlich, and other methods, to determine whether nerve-fibres could be demonstrated in them. None were found. It is probable that the blood-supply to the brain is regulated through the bulbar vaso-constrictor centre.[3] Anæmia or asphyxia of the brain stimulates the cells composing this centre, vascular constriction of many vessels follows, and more blood enters the cranial cavity. The vessels of the splanchnic area play a chief part in this regulative process.[4] Their importance to the circulation in the brain is shown by the fatal effect of the section of the splanchnic nerves in the rabbit. On placing the animal on its feet, so much blood flows into the relaxed abdominal vessels that death may follow from anæmia of the brain.

[1] Bayliss and Hill, 1895, p. 337. [2] Gulland, 1895, p. 361.
[3] Bayliss and Hill, 1895, p. 358. [4] Wertheimer, 1893, p. 297.

Vaso-motor Nerves of Head.—The cervical sympathetic contains vaso-constrictor fibres for the corresponding side of the face, the eye, ear, salivary glands[1] and tongue, and possibly the brain. The spinal vaso-constrictor fibres for the vessels of the head in the cat and dog leave the cord in the first five thoracic nerves;[2] in the rabbit, in the second to eighth thoracic, seven in all.[3]

Vaso-dilator fibres for the face and mouth have been found in the cervical sympathetic by Dastre and Morat,[4] leaving the cord in the second to fifth dorsal nerves, and uniting (at least for the most part) with the trigeminus by passing, according to Morat,[5] from the superior cervical sympathetic ganglion to the ganglion of Gasser. Other dilator fibres for the skin and mucous membrane of the face and mouth arise apparently in the trigeminus, for the stimulation of this nerve between the brain and Gasser's ganglion causes dilatation of the vessels of the face,[6] and in the nerve of Wrisberg.[7]

The vaso-motor nerves of the tongue have been recently studied by Isergin.[8] The lingual and the glosso-pharyngeal nerves are recognized by all authors as dilators of the lingual vessels. The sympathetic and the hypoglossus contain constrictor fibres for the tongue. It is possible that the lingual contains also a small number of constrictor fibres. Most if not all these vaso-motor fibres arise in the sympathetic and reach the above-mentioned nerves by way of the superior cervical ganglion.[9] They degenerate in from three to five weeks after the extirpation of the ganglion.

Morat and Doyon[10] cut the cervical sympathetic in a curarized rabbit and examined the retinal arteries with the ophthalmoscope. They were found dilated. The excitation of the cervical sympathetic caused constriction, the excitation of the thoracic sympathetic dilatation of these vessels. The retinal fibres leave the sympathetic at the superior cervical ganglion and pass along the communicating ramus to the ganglion of Gasser, whence they reach the eye through the ophthalmic branch of the fifth nerve, the gray root of the ophthalmic ganglion, and the ciliary nerves. Most, or all, of the fibres for the anterior part of the eye are found in the fifth nerve.

Lungs.—The methods ordinarily employed for the demonstration of vaso-motor nerves cannot without danger be used in the study of the innervation

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[1] Compare Vulpian, 1885, p. 853.   [2] Langley, 1892, p. 102.

[3] Langley, 1892, p. 104.

[4] Dastre and Morat, 1884, pp. 116, 129; see also Pye-Smith, 1887, p. 25; Langley, 1890, p. 146; Langley and Dickinson, 1890, p. 380; Morat, 1891, p. 87; Piotrowski, 1892, p. 464; Langley, 1892, p. 97.

[5] Morat, 1889, p. 201.

[6] Vulpian, 1885, p. 982; compare Dastre and Morat, 1884, p. 118; Langley, 1893, iv.; Piotrowski, 1894, p. 278.

[7] Vulpian, 1885, p. 1038.

[8] Isergin, 1894, p. 441; other literature: Anrep and Cybulski, 1884; Vulpian, 1885, pp. 854, 1038; Piotrowski, 1887, p. 454; 1894, p. 246.

[9] For evidence that probably all vaso-constrictor fibres to the head (nerve-cells of the second class) end in the superior cervical ganglion, see Langley and Dickinson, 1889, p. 425.

[10] Morat and Doyon, 1892, p. 60; see also Langley, 1893, iv.; Doyon, 1890, p. 774; 1891, p. 154.

of the pulmonary vessels.[1] A fall in the blood-pressure in the pulmonary artery, for example, produced by stimulating any nerve cannot be taken as final evidence that the stimulation caused the constriction of the pulmonary vessels. The lesser circulation is so connected that changes in the calibre of the vessels of a distant part, the liver for example, may alter the quantity of blood in the lungs.[2] The method of Cavazzani[3] avoids these difficulties. Cavazzani establishes an artificial circulation through one lobe of a lung in a living animal, and measures the outflow per unit of time. An increase in the outflow means a dilatation of the vessels, diminution means constriction. He finds that the outflow diminishes in the rabbit when the vagus is stimulated in the neck, and increases when the cervical sympathetic is stimulated. Franck measures the pressure simultaneously in the pulmonary artery and left auricle, a method apparently also trustworthy. The stimulation of the inner surface of the aorta causes a rise of pressure in the pulmonary artery and a simultaneous fall in the left auricle, indicating, according to Franck,[4] the vaso-constrictor power of the sympathetic nerve over the pulmonary vessels. A reflex constriction is also produced by the stimulation of the central end of a branch
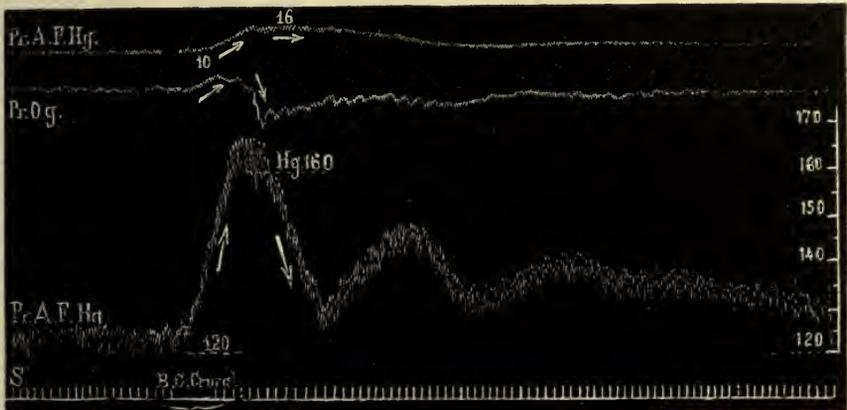
Fig. 130.—The excitation of the central end of the inguinal branch of the crural (sciatic) nerve causes a rise in the aortic pressure (*Pr.A.F.*), a rise in the pressure in the pulmonary artery (*Pr.A.P.*) of 10 to 16 mm. Hg, accompanied by a falling pressure in the left auricle (*Pr.O.G.*) (Franck, 1896, p. 184). The rise of pressure in the pulmonary artery, together with the fall in the left auricle, demonstrate, according to Franck, a constriction of the pulmonary vessels.

of the sciatic, intercostal, abdominal pneumogastric, and abdominal sympathetic nerves[5] (see Fig. 130).

Heart.—Vaso-motor fibres for the coronary arteries of the heart have been described in the vagus of the dog[6] and cat.[7]

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[1] Literature: Openchowski, 1882, p. 233; Franck, 1889, p. 555; Bradford and Dean, 1889, i.-iv.; 1889, p. 369; Couvreur, 1889, p. 731; Franck, 1890, p. 550; Arthaud and Butte, 1890, p. 12; Knoll, 1890, p. 13; Cavazzani, 1891, p. 32; Doyon, 1893, p. 101; Henriques, 1893, p. 229; Bradford and Dean, 1894, p. 34; Franck, 1895, pp. 744, 816; 1896, p. 178.

[2] Tigerstedt, 1893, p. 493.   [3] Cavazzani, 1891, p. 35.

[4] Franck, 1896, p. 178.   [5] Franck, 1896, p. 184.

[6] Martin, 1891, p. 291.   [7] Porter, 1896, p. 39.

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Intestines.[1]—The mesenteric vessels receive vaso-constrictor fibres from the sympathetic chiefly through the splanchnic nerve.[2]   The vaso-constrictors of the jejunum, as a rule, begin to be found in the rami of the fifth dorsal nerves ; a little lower down, those for the ileum come off; and still lower down, those for the colon ; none arise below the second lumbar pair.[3]   According to Hallion and Franck, vaso-dilator fibres are present in the same sympathetic nerves that contain vaso-constrictors.   The dilator fibres are most abundant or most powerful in the rami of the last three dorsal and first two lumbar nerves. There is some evidence of the presence of vaso-dilator fibres in the vagus. The excitation of the vaso-constrictor centres by the blood in asphyxia produces constriction of the abdominal vessels.[4]   The vaso-dilator as well as the vaso-constrictor fibres of the splanchnic probably end in the solar and renal plexuses.[5]

Liver.—Cavazzani and Manca[6] have recently attempted to show the presence of vaso-motor fibres in the liver.   Their method consists in passing warm normal saline solution from a Mariotte's flask at a pressure of 8 to 10 millimeters Hg through the hepatic branches of the portal vein and measuring the outflow in a unit of time from the ascending vena cava.   On stimulating the splanchnic nerve they observed that the outflow was usually diminished though sometimes increased, indicating perhaps that the splanchnics contain both vaso-constrictor and vaso-dilator fibres for the hepatic branches of the portal vein.   The vagus appeared to contain vaso-dilator fibres.   Further studies are necessary, however, before pronouncing definitely upon these questions.

Kidney.[7]—The vaso-motor nerves of the kidney leave the cord from the sixth dorsal to the second lumbar nerve.[8]   In the dog, most of the renal vaso-motor fibres are found in the eleventh, twelfth, and thirteenth dorsal nerves.[9] The stimulation of the nerves entering the hilus of the kidney between the artery and vein causes a marked and sudden renal contraction, but the organ soon regains its former volume.[10]   Constriction follows also the stimulation of the peripheral end of the cut splanchnic nerve.[11]   Bradford has demonstrated renal vaso-dilator fibres for certain nerves by stimulating at the rate of one induction shock per second.   For example, the excitation of the thirteenth dorsal nerve with 50 to 5 induction shocks per second gave always a constric-

[1] Literature: Cyon and Ludwig, 1866, p. 136 ; Cohnheim and Roy, 1883, p. 440: Dastre and Morat, 1884, p. 294 ; Waters, 1885, p. 460 ; Bradford, 1889, p. 390 ; Hallion and Franck, 1896, p. 478.   [2] Cyon and Ludwig, 1866, p. 136.

[3] Hallion and Franck, 1896, p. 496.

[4] Dastre and Morat, 1884, p. 294 ; Hallion and Franck, 1896, p. 506.

[5] Langley and Dickinson, 1889, p. 429.

[6] Cavazzani and Manca, 1895, p. 33: see also Pal, 1888, p. 73.

[7] Literature : Nicolaides, 1882, p. 28 ; Cohnheim and Roy, 1883, p. 345 ; Klemensiewicz, 1886, p. 84 ; Masius, 1888, p. 539 ; Bradford, 1889, p. 404 ; Arthaud and Butte, 1890, p. 379 ; Preobraschensky, 1892 ; Wertheimer, 1893, p. 1024 ; 1894, p. 308 ; Bayliss and Bradford, 1894, p. 17.   [8] Bayliss and Bradford, 1894, p. 17.   [9] Bradford, 1889, p. 404.

[10] Cohnheim and Roy, 1883, p. 345 ; and Bradford, 1889, p. 364.

[11] Cohnheim and Roy, 1883, p. 440.

tion of the kidney, but when a single shock per second was employed, the kidney dilated.[1] If the cells connected with the renal vaso-motor fibres are stimulated directly by venous blood as in asphyxia, the animal being curarized, a decided constriction of the kidney results.[2] The reflex excitation of these cells is of especial importance. The stimulation of the central end of the sciatic or the splanchnic nerves causes renal constriction.[3] The same effect is easily produced by stimulating the skin, for example, by the application of cold.[4] The stimulation of the sole of the foot in a curarized dog caused contraction of the renal vessels.[5] There is some evidence that the splanchnic vaso-motor fibres for the kidney end in the cells of the renal plexus.[6]

Spleen.—The stimulation of the peripheral end of the splanchnic nerves causes a sudden and large diminution in the volume of the spleen.[7] It is, however, not certain whether the constriction of the spleen is to be referred primarily to a constriction of its blood-vessels or to the contraction of the intrinsic muscular fibres which play so large a part in the changes of volume of this organ. The doubt is strengthened by the fact that section of the splanchnic nerves does not alter the volume of the spleen; dilatation would be expected were these nerves the pathway of vaso-constrictor fibres for the spleen.

External Generative Organs.[8]—The recent history of the vaso-motor nerves of the external generative organs—namely, those developed from the urogenital sinus and the skin surrounding the urogenital opening[9]—begins with Eckhard,[10] who showed that the stimulation of certain branches of the first and second, and occasionally the third, sacral nerves (dog) caused a dilatation of the blood-vessels of the penis and erection of that organ, and with Goltz,[11] who found an erection centre in the lumbo-sacral cord. Numerous researches in recent years, among which the reader is referred especially to the work of Langley and Langley and Anderson,[12] have shown that the vaso-motor nerves of the external generative organs of both sexes may be divided into a lumbar and a sacral group.

The *lumbar fibres* pass out of the cord in the anterior roots of the second, third, fourth, and fifth lumbar nerves, and run in the white rami communicantes to the sympathetic chain, from which they reach the periphery either by way of the pudic nerves or by the pelvic plexus. The greater number take

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[1] Bradford, 1889, p. 387.   [2] Cohnheim and Roy, 1883, p. 437.

[3] Cohnheim and Roy, 1883, p. 439.

[4] Preobraschensky, 1892; Wertheimer, 1894, p. 308.   [5] Wertheimer, 1893, p. 1024.

[6] Langley and Dickinson, 1889, p. 429.

[7] Roy, 1882, p. 225; Schäfer and Moore, 1896, pp. 229, 287.

[8] Literature: Goltz and Freusberg, 1874, p. 460; Kaes, 1883, p. 1; Anrep and Cybulski, 1884; Gaskell, 1887, iv.; Morat, 1890, p. 480; Piotrowski, 1892, p. 464; Sherrington, 1892, p. 686; Franck, 1894, p. 740; Piotrowski, 1894, p. 284; Franck, 1895, p. 122; Langley and Anderson, 1895, p. 5; 1895, p. 76.

[9] Langley and Anderson, 1895, p. 76; 1895, p. 85.   [10] Eckhard, 1863, p. 145.

[11] Goltz and Freusberg, 1874, p. 460.   [12] Langley and Anderson, 1895, p. 120.

the former course, running down the sympathetic chain to the sacral ganglia, and passing from these ganglia through the gray rami communicantes to the sacral nerves. None of the fibres thus derived enter the nervi erigentes of Eckhard. Of the various branches of the pudic nerves (rabbit), the nervus dorsalis causes constriction of the blood-vessels of the penis and the perineal nerve contraction of the blood-vessels of the scrotum. The course by way of the pelvic plexus is taken by relatively few fibres. They run for the most part in the hypogastric nerves, a few sometimes joining the plexus from the lower lumbar or upper sacral sympathetic chain, or from the aortic plexus. The presence of vaso-dilator fibres in the lumbar group is disputed.[1]

The *sacral group* of nerves leave the spinal cord in the sacral nerve roots. Their stimulation causes dilatation of the vessels of the penis and vulva.

Internal Generative Organs (those developed from the Müllerian, or the Wolffian, ducts).—Langley and Anderson[2] find vaso-constrictor fibres for the Fallopian tubes, uterus, and vagina in the female, and the vasa deferentia and seminal vesicles in the male, in the second, third, fourth, and fifth lumbar nerves. The internal generative organs receive no afferent, and probably no efferent, fibres from the sacral nerves.[3]

The position of the sympathetic ganglion-cells, the processes of which carry to their peripheral distribution the efferent impulses brought to them by the efferent vaso-motor fibres of the spinal cord, may be determined by the *nicotin method* of Langley. About 10 milligrams of nicotin injected into a vein of a cat prevent for a time, according to Langley,[4] any passage of nerve-impulses through a sympathetic cell. Painting the ganglion with a brush dipped in nicotin solution has a similar effect. The fibres peripheral to the cell, on the contrary, are not paralyzed by nicotin. Now, after the injection of nicotin the stimulation of the lumbar nerves in the spinal canal has no effect on the vessels of the generative organs.[5] Hence all the vaso-motor fibres of the lumbar nerves must be connected with nerve-cells somewhere on their course. The lumbar fibres which run outward to the inferior mesenteric ganglia are for the most part connected with the cells of these ganglia. A lesser number is connected with small ganglia lying as a rule near the organs to which the nerves are distributed. The remaining division of lumbar fibres running downward in the sympathetic chain, and including the majority of the nerve-fibres to the external generative organs are connected with nerve-cells in the sacral ganglia of the sympathetic.

The sacral group of nerves enter ganglion-cells scattered on their course, most of the nerve-cells for any one organ being in ganglia near that organ.

Bladder.—Neither lumbar nor sacral nerves send vaso-motor fibres to the vessels of the bladder.[6]

[1] Franck, 1895, p. 143; Langley and Anderson, 1895, p. 93.
[2] Langley and Anderson, 1895, p. 129.   [3] Langley and Anderson, 1896, p. 372.
[4] Langley, 1894, p. 420, also Langley and Dickinson, 1889, p. 423.
[5] Langley and Anderson, 1895, p. 131.   [6] Langley and Anderson, 1895, p. 84.

Portal System.—It has already been said that vaso-constrictor fibres for the portal vein were discovered by Mall[1] in the splanchnic nerve. Constrictor fibres have been found by Bayliss and Starling[2] in the nerve-roots from the third to the eleventh dorsal inclusive. Most of the constrictor nerves pass out from the fifth to the ninth dorsal.

Back.—The dorsal branches of the lumbar and intercostal arteries, issuing from the dorsal muscles to supply the skin of the back,[3] can be seen to contract when the gray ramus of the corresponding sympathetic ganglia are stimulated.

Limbs.[4]—The vaso-motor nerves of the limbs in the dog leave the spinal cord from the second dorsal to the third lumbar nerves.[5] The area for the hind limb, according to Bayliss and Bradford,[6] is less extensive than that for the fore limb, the former receiving constrictor fibres from nine roots, namely the third to the eleventh dorsal, the latter from six roots, the eleventh dorsal to third lumbar. Langley[7] finds that the sympathetic constrictor and dilator fibres for the fore foot are connected with nerve-cells in the ganglion stellatum; while those for the hind foot are connected with nerve-cells in the sixth and seventh lumbar, and the first, and possibly the second, sacral ganglia.

Tail.[8]—Stimulation of any part of the sympathetic from about the third lumbar ganglion downward almost completely stops the flow of blood from wounds in the tail. The vaso-motor fibres for the tail leave the cord chiefly in the third and fourth lumbar nerves. Their stimulation may cause primary dilatation followed by constriction.

Muscles.[9]—According to Gaskell,[10] the section of the nerve belonging to any particular muscle or group of muscles causes a temporary increase in the amount of blood which flows from the muscle vein. The stimulation of the peripheral end of the nerve also increases the rate of flow through the muscle. The same increase is seen on stimulation of the nerve when the muscle is kept from contracting by curare, provided the drug is not used in amounts sufficient to paralyze the vaso-dilator nerves.[11] Mechanical stimulation by crimping the peripheral end of the nerve gives also an increase.[12] The existence of vaso-dilator nerves to muscles must therefore be conceded. The presence of vaso-constrictor fibres is shown by the diminution in outflow from the left femoral vein which followed Gaskell's stimulation of the peripheral end of the abdominal sympathetic in a thoroughly curarized dog,[13] but the supply of constrictor fibres

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[1] Mall, 1890, p. 57; 1892, p. 409.   [2] Bayliss and Starling, 1895, p. 125.

[3] Langley, 1895, p. 314.

[4] Literature: Lewaschew, 1882, p. 389; 1884; Laffont, 1882, p. 864; Bowditch and Warren, 1886, p. 416; Humilewski, 1886, p. 126; Langley, 1891, p. 375; Jegorow, 1892, p. 69; Piotrowski, 1892, p. 464; Thompson, 1893, p. 104; Langley, 1893, p. 227; Piotrowski, 1894, p. 258; Wertheimer, 1894, p. 724; Bayliss and Bradford, 1894, p. 16; Langley, 1895, p. 307.

[5] Bayliss and Bradford, 1894, p. 22.

[6] Bayliss and Bradford, 1894, pp. 16, 17; compare Langley, 1895, p. 307.

[7] Langley, 1891, p. 375.   [8] Langley, 1895, p. 311.

[9] Literature: Sadler, 1869, p. 77; Gaskell, 1876, p. 45; 1877, pp. 360, 720; Grützner and Heidenhain, 1878, p. 1; Gaskell, 1878, p. 262.

[10] Gaskell, 1878, p. 262.   [11] *Ibid.*, p. 274.   [12] *Ibid.*, p. 275.   [13] *Ibid.*, p. 277.

is comparatively small.   In curarized animals reflex dilatation apparently follows the stimulation of the nerves the excitation of which would have caused the contraction of the muscles observed, had not the occurrence of actual contraction been prevented by the curare.   The stimulation of the central end of nerves not capable of calling forth reflex contractions in the muscles observed —for example, the vagus—seems to cause constriction of the muscle-vessels.[1]

[1] Gaskell, 1878, p. 289.

VIII. RESPIRATION.

A STUDY of the phenomena of animal life teaches us that a supply of oxygen and an elimination of carbon dioxide are essential to existence. Oxygen is indispensable to life; carbon dioxide is inimical to life. One serves for the disintegration of complex molecules whereby energy is evolved, while the other is one of the main effete products of this dissociation. We therefore find an intimate relationship between the ingress of the one and the egress of the other. During the entire life of the individual there is this continual interchange, which we term *respiration*. This term embraces two acts which, while different, are nevertheless co-operative—first, the interchange of O and CO_2; second, the movements of certain parts of the body, having for their object the inflow and outflow of air to and from the lungs. The former, properly speaking, is *respiration;* the latter, *movements of respiration.*

Respiration is spoken of as *internal* and as *external* respiration. In the very lowest forms of life the interchange of gases takes place directly between the various parts of the organism and the air or the water in which the organism lives; but in higher beings a circulating fluid becomes a means of exchange between the bodily structures and the surrounding medium, so that in these beings there is first an interchange between the air or the water in which the animal lives and the circulating medium, and subsequently an interchange between the circulating medium and the tissues. Therefore in the most primitive forms of life respiration is a single process, while in higher organisms it is a dual process, or one consisting of two stages, the first being the interchange between the atmosphere or the water surrounding the body and the circulating medium, and the second between the circulating medium and the bodily structures. In man, external respiration is the interchange taking place between the blood and the gases in the lungs and between the blood and the air through the skin; while internal respiration is the interchange between the blood and the tissues. In external respiration O is absorbed and CO_2 is given off by the blood; in internal respiration the blood absorbs CO_2 and gives off O.

A. THE RESPIRATORY MECHANISM IN MAN.

The respiratory apparatus in man consists (1) of the lungs and the air-passages leading to them, the thorax and the muscular mechanisms by means of which the lungs are inflated and emptied, and the nervous mechanisms connected therewith; and (2) the skin, which, however, plays a subsidiary part in man, and need not here be considered.

The lungs may be regarded as two large bags broken up into saccular divisions and subdivisions which ultimately consist of a vast number of little pouches, or infundibuli, each of which is, as the name implies, funnel-shaped, the walls being hollowed out into alveoli, or air-vesicles. These alveoli vary in size from $120\,\mu$ to $380\,\mu$, the average diameter being about $250\,\mu$ ($\frac{1}{100}$ inch). Each infundibulum communicates by means of a small air-passage with a bronchiole, which in turn communicates with a smaller air-tube or bronchus, and finally, through successive unions, with the common air-duct or trachea. It is estimated that the alveoli number about 725,000,000, and that the total superficies exposed by them to the gases in the lungs is about 200 square meters, or from one hundred to one hundred and thirty times greater than the surface of the body (1.5 to 2 square meters). The wall of each alveolus forms a delicate partition between the air in the lungs and an intricate network of blood-vessels; this network is so dense that the spaces between the capillaries are, as a rule, smaller than the diameters of the vessels. The lungs, therefore, are exceedingly vascular, and it is estimated that the vessels contain on an average about 1.5 kilograms of blood. Owing to the minuteness of the capillaries and the density of the network, the air-cells may be said to be surrounded by a film of blood which is about $10\,\mu$ in thickness and has an area of about 150 square meters.

The lungs are highly elastic, and their elasticity is perfect, as is shown by the fact that they immediately regain their passive condition as soon as the dilating or distending force has been removed. Before birth the lungs are airless (*atelectatic*) and the walls of the bronchioles and the infundibuli are in contact, yet in the child before birth, as in the adult, the lungs are in apposition with the thoracic walls, being separated only by two layers of the pleuræ. As soon as the child is born a few respiratory movements are sufficient to inflate them, and thereafter they never regain their atelectatic condition, since after the most complete collapse, such as occurs when the thorax is opened, some air remains in the alveoli, owing to the fact that the walls of the bronchioles come together before all of the air can escape. As the child grows the thorax increases in size more rapidly than the lungs, and becomes too large, as it were, for the lungs, which, as a consequence, become permanently distended because of their being in an air-tight cavity. If the chest of a cadaver be punctured, the lungs immediately shrink so that a considerable air-space will be formed between them and the walls of the thorax. This collapse is due to the condition of elastic tension which exists from the moment air is introduced into the alveoli, and which increases with the degree of expansion. Therefore, after the lungs are inflated they exhibit a persistent tendency to collapse; consequently they must exercise upon the thoracic walls and diaphragm a constant traction or "pull" which is in proportion to the amount of tension. It is therefore obvious that there must exist within the thorax, under ordinary circumstances, a state of *negative* pressure (pressure below that of the atmosphere). This can be proven by connecting a trocar with a manometer and then forcing the trocar into one of the pleural sacs.

Donders found that the pressure at the end of quiet expiration was −6 millimeters of Hg, and at the end of quiet inspiration −9 millimeters. According to these figures, the pressure on the heart, great blood-vessels, and other thoracic structures lying between the lungs and the thoracic walls would be 754 millimeters of Hg (one atmosphere, 760 millimeters, −6 millimeters) at the end of quiet expiration, and 751 millimeters of Hg at the end of quiet inspiration. Corresponding values by Hutchinson are −3 millimeters and −4.5 millimeters. Arron[1] found in a case of a woman with emphysema that the pressure at the end of expiration ranged from −1.9 to −3.9 millimeters, and at the end of inspiration from −4 to −6.85 millimeters, according to the position of the body, the pressure being lowest in the lying posture, higher when sitting in bed, still higher when sitting on a chair, and highest when sitting and when inspiration on the well side was hindered, thus throwing a larger portion of the work on the diseased side, on which the measurements were made. During inspiration negative pressure increases in proportion to the depth of inspiration—or, in other words, in relation to the amount of expansion of the lungs—while during expiration it gradually falls to the standard at the beginning of inspiration. During forced inspiration it may reach −30 to −40 millimeters or more. The pressure thus observed within the thorax (*outside* of the lungs) is known as *intrathoracic* pressure, and must not be confounded with *intrapulmonary* or *respiratory* pressure, which exists *within* the lungs and the respiratory passages (see p. 516).

The thorax is capable of enlargement in all directions. It is cone-shaped, the top of the cone being closed in by the structures of the neck; the sides, by the vertebral column, ribs, costal cartilages, sternum, and intercostal sheets of muscular and other tissues; and the bottom, by the arched diaphragm. It is obvious that, since the thorax is an air-tight cavity and completely filled by various structures, enlargement in any direction must cause a diminution of pressure within the lungs, while a shrinkage would operate to bring about an opposite condition of increased pressure. Since the trachea is the only means of communication between the lungs and the atmosphere, it is evident that such alterations in pressure must encourage either the inflow or the outflow of air, as the case may be; consequently, when the thoracic cavity is expanded the pressure within the lungs is less than that of the atmosphere, and air is forced into the lungs; and when the thorax is decreased in size the reverse of the above pressure relation exists, and the air is expelled. In fact, the thorax and the lungs behave as a pair of bellows—just as air is drawn into the expanding bellows, so is air drawn into the lungs by the enlargement of the thorax; similarly, as the air is forced from the bellows by compression, so is air forced from the lungs by the shrinkage of the lungs and the thorax.

During the expansion of the thorax the lungs are entirely passive, and by virtue of their perfect elasticity merely follow the thoracic walls, from which they are separated only by the two layers of the pleuræ, which, being moistened with lymph, slide over each other without appreciable friction. That

[1] *Virchow's Archiv*, 1891, vol. 126, p. 523.

the lungs are entirely passive is shown by the fact that when the thorax is punctured, so as to allow a free communication with the atmosphere, expansion of the chest is no longer followed by dilatation of the lungs. During the shrinkage of the thorax the elastic reaction of the lungs plays an active part.

Respiration, Inspiration, and Expiration.—Each respiration or respiratory act consists of an *inspiration* (enlargement of the thorax and inflation of the lungs) and an *expiration* (shrinkage of the thorax and the lungs). According to some observers, a *pause* exists after expiration (*expiratory pause*), but during quiet breathing no such interval can be detected. A pause may be present when the respirations are deep and infrequent. Under certain abnormal circumstances a pause may exist between inspiration and expiration (*inspiratory pause*).

Inspiration is accomplished by the contraction of certain muscles which are designated *inspiratory muscles*. Expiration during quiet breathing is essentially a passive act, but during forced breathing various muscles are active; these muscles are distinguished as *expiratory muscles*.

During inspiration the thorax is enlarged in the vertical, transverse, and antero-posterior diameters. During quiet breathing the vertical diameter is increased by the descent of the diaphragm, and during deep inspiration it is further increased by the backward and slightly downward movement of the floating ribs, and by the extension of the vertebral column, which raises the sternum with its costal cartilages and ribs. The transverse diameter is increased by the elevation and eversion (rotation outward and upward) of the ribs. The antero-posterior diameter is increased by the upward and outward movement of the sternum, costal cartilages, and ribs. During quiet inspiration in men the sternum is not raised to a higher level, but the lower end is rotated forward and upward. It is only during deep inspiration in the male and in quiet or deep inspiration in women that the sternum as a whole is elevated.

The movements of the anterior and lateral walls constitute *costal* respiration, and those of the diaphragm *diaphragmatic* or, as it is sometimes called, *abdominal* respiration, since the descent of the diaphragm causes protrusion of the abdominal walls. Both types coexist during ordinary respiratory movements, but one may be more prominent than the other. The costal type is well marked in women, and the diaphragmatic type in men. These peculiarities are not, however, due to inherent sexual differences, but to dress and heredity. Young children of both sexes exhibit, as a rule, the diaphragmatic type, and it is only near or at puberty that the costal type is developed in the female.

The chief muscles of inspiration are the *diaphragm*, the *quadrati lumborum*, the *serrati postici inferiores*, the *scaleni*, the *serrati postici superiores*, the *levatores costarum longi et breves*, and the *intercostales externi et intercartilaginei*.

Movements of the Diaphragm.—The *diaphragm* is attached by its two crura to the first three or four lumbar vertebræ, to the lower six or seven costal cartilages and adjoining parts of the corresponding ribs, and to the posterior surface of the ensiform appendix. It projects into the thoracic cavity in the form of a flattened dome, the highest part being formed by the central

tendon. The tendon consists of three lobes which are partially separated by depressions. The right lobe, or largest, is the highest portion and lies over the liver; the left lobe, which is the smallest, lies over the stomach and the spleen; while the central lobe is situated anteriorly, the upper surface blending with the pericardium. The central tendon is a common point of insertion of all the muscular fibres of the diaphragm. In the passive condition the lower portions of the diaphragm are in apposition to the thoracic walls. During contraction the whole dome is drawn downward, while the parts of the muscle in contact with the chest are pulled inward. According to Hultkranz, the cardiac part of the diaphragm descends from 5.5 to 11.5 millimeters during quiet inspiration, and as much as 42 millimeters during deep inspiration. Not only is the height of the arch lessened, but there is also a tendency, owing to the points of attachment of the diaphragm, toward the pulling of the lower ribs with their costal cartilages and the lower end of the sternum inward and upward; this traction, however, is counterbalanced by the pressure of the abdominal viscera, the latter being forced downward and outward against the thoracic and abdominal walls. If this counterbalancing pressure be removed by freely opening the abdominal cavity, especially after removing the viscera, the lower lateral portions of the thorax will be seen during each inspiration to be drawn inward. It is during labored inspiration only that this movement occurs in the intact individual.

When the diaphragm ceases to contract, the negative intrathoracic pressure is sufficient to draw the sunken dome upward into the passive position. This upward movement of the diaphragm is aided by the positive intra-abdominal pressure exerted by the elastic tension of the abdominal walls through the medium of the abdominal viscera. In forced expiration the contraction of the abdominal muscles (p. 515) adds additional force.

The *quadrati lumborum* are believed to assist the diaphragm by fixing the twelfth ribs, or even lowering them during deep inspiration. Each of these muscles arises from the ilio-lumbar ligament and the iliac crest, and is inserted into the transverse processes of the first, second, third, and fourth lumbar vertebræ and the lower border of one-half of the length of the last rib. These muscles are regarded by some physiologists as expiratory agents.

The *serrati postici inferiores* similarly assist the diaphragm by drawing the lower four ribs backward, and in deep inspiration also downward. They not only thus oppose the tendency of the diaphragm to pull the lower ribs upward, which would lessen its effectiveness in enlarging the vertical diameter of the thorax, but they contribute to this enlargement by their downward and backward traction upon the ribs and the attached portions of the diaphragm. These muscles pass from the spines of the eleventh and twelfth dorsal and first two or three lumbar vertebræ and the supraspinous ligament to the lower borders of the ninth, tenth, eleventh, and twelfth ribs, beyond their angles.

Simultaneously with the contraction of the diaphragm the thoracic walls

are drawn upward and outward by the contractions of other inspiratory muscles, thus enlarging the thorax in the antero-posterior and lateral diameters.

Movements of the Ribs.—The movements of the ribs during inspiration are, as a whole, essentially rotations upward and outward upon axes which are directed obliquely outward and backward, each axis being directed through the costo-vertebral articulation and a little anterior to the costo-transverse articulation.   The vertebral ends of the ribs lie higher than their sternal extremities, so that when the ribs are elevated the anterior ends are advanced forward and upward.   The arches of the ribs are inclined downward and outward, and, owing to the obliquity of the axes of rotation, the convexities are rotated upward and outward, or everted.   Thus both the antero-posterior and lateral diameters are increased.

The degree of obliquity of the axes of rotation of the different ribs varies. The axis of the first rib is almost transverse (Fig. 131), while that of each succeeding rib to the ninth, inclusive, becomes more oblique (Fig. 132).   The
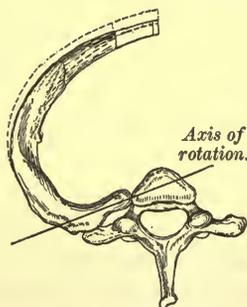
FIG. 131.—First dorsal vertebra and rib.   FIG. 132.—Sixth dorsal vertebra and rib.
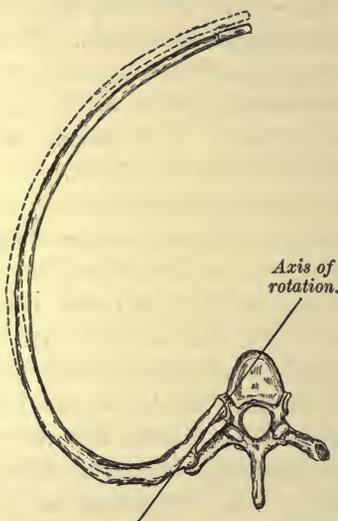
more oblique the axis, the greater the degree of eversion; consequently the first rib is capable of but slight eversion, while the lower ribs may be everted to a relatively marked extent.   Moreover, the peculiarities or the absence of the costo-transverse articulations materially affect the character of the movements of the different ribs.   Thus, the facets on the transverse processes of the first and second dorsal vertebræ are cup-shaped, and into them are inserted the conical tuberosities of the ribs, thus materially limiting the rotation of the ribs; while the facets for the articulations of the third to the tenth ribs, inclusive, assume a plane character which admits of larger movement.   The facets for the third to the fifth ribs are almost vertical, thus allowing a free movement upon the oblique axis; while the facets for the sixth to the ninth ribs, inclusive, are directed obliquely upward and backward, and admit of a move-

ment upward and backward as well as a rotation upon the oblique axis. Finally, the eleventh and twelfth ribs (and generally the tenth) have no costo-transverse articulations, allowing a movement backward and forward as well as rotation upon their oblique axes. While, therefore, the movements of the ribs are essentially rotations upward, forward, and outward upon oblique axes directed through the costo-vertebral articulations and a little anterior to the costo-transverse articulation, they are more or less modified by reason of the motion permitted by the nature or the absence of the costo-transverse articulations. Thus, the essential character of the movement of the first to the fifth ribs is a rotation upward, forward, and outward; that of the sixth to the ninth ribs, a rotation upward, forward, and outward combined with a movement upward and backward; that of the tenth and eleventh ribs, a rotation upward, forward, and outward with a rotation backward; that of the twelfth rib, chiefly a rotation backward and rather downward. The character of the movement of each rib differs somewhat as we pass from the first to the twelfth ribs.

During forced inspiration the sternum and its attached costal cartilages with their ribs are pulled upward and outward, while the ninth, tenth, eleventh, and twelfth ribs are drawn backward and downward. During expiration these movements are of course reversed.

The intercostal spaces during inspiration, except the first two, are widened.[1] The reason for this opening out must be apparent when we remember that the ribs are arranged in the form of a series of parallel curved bars directed obliquely downward, and the fact may be demonstrated by means of a very simple model (Fig. 133) consisting of a vertical support and two parallel bars, *a, b,* placed obliquely. If, after measuring the distance *c, d,* we raise the bars to a horizontal position, the distance *e, f* will be found to be greater than *c, d,* since the bars rotate around fixed points placed in the same vertical line. This widening of the intercostal spaces is readily accomplished because of the elasticity of the costal cartilages.

The muscles involved in the movements of the ribs during quiet inspiration include the *scaleni,* the *serrati postici superiores,* the *levatores costarum longi et breves,* and the *intercostales externi et intercartilaginei.*

FIG. 133.—Model to illustrate the widening of the intercostal spaces during inspiration.

The *scaleni* are active in fixing the first and second ribs, thus establishing, as it were, a firm basis from which the external intercostal muscles may act. The scalenus anticus passes between the tubercles of the transverse processes of the third, fourth, fifth, and sixth cervical vertebræ to the scalene tubercle on the first rib. The scalenus medius passes from the posterior tubercles of the transverse processes of the lower six cervical vertebræ to the upper surface of the first rib, extending from the tubercle to just behind the groove for the subclavian artery. The scalenus posticus passes from the transverse pro-

[1] Ebner: *Archiv für Anatomie und Physiologie*, Anatomische Abtheilung, 1886, p. 199.

cesses of the two or three lower cervical vertebræ to the outer surface of the second rib.

The *serrati postici superiores* aid in fixing the second ribs and raise the third, fourth, and fifth ribs. The muscles pass from the ligamentum nuchæ and the spines of the seventh cervical and first two or three dorsal vertebræ to the upper borders of the second, third, fourth, and fifth ribs, beyond their angles.

The *levatores costarum breves* consist of twelve pairs which pass from the tips of the transverse processes of the seventh cervical and first to the eleventh dorsal vertebræ downward and outward, each being inserted between the tubercle and the angle of the next rib below. Those arising from the lower ribs send fibres to the second rib below (*levatores costarum longiores*). They assist in the elevation and eversion of the first to the tenth ribs, inclusive, and co-operate with the quadrati lumborum and the serrati postici inferiores to draw the lower ribs backward.

The functions of the *intercostales* have been a matter of dispute for centuries, and the problem is still unsettled. For instance, Galen looked upon the external intercostals as being expiratory. Vesalius asserted that both the external and the internal intercostals are expiratory, while Haller expressed the opposite belief. Hamberger and Hutchinson regarded the external intercostals and the interchondrals as being inspiratory, and the interosseous portion of the internal intercostals as being expiratory. Finally, Landois believes that while the external intercostals and the interchondrals are active during inspiration, and the interosseous portion of the internal intercostals during expiration, their chief actions are not to enlarge nor to diminish the volume of the thoracic cavity, but to maintain a proper degree of tension of the intercostal spaces. Each view still has its adherents.

The actions of the intercostal muscles are generally demonstrated by means of rods and elastic bands arranged in imitation of the ribs and the origins and insertions of the muscles, or by geometric diagrams. The well-known model of Bernouilli consists of a vertical bar representing the vertebral column, upon which bar move two parallel straight rods in imitation of the ribs (Fig. 134). If the rods be placed at an oblique angle and a tense rubber band (a, b) be affixed to represent the relations of the external intercostals, the rods will be pulled upward and the space between them will be widened. The interchondral portion of the internal intercostals bears the same oblique relation to the costal cartilages, and theoretically should have the same action. The action of the interosseous portion of the internal intercostals is demonstrated in this way: If the rubber band be placed at right angles to the rods (Fig. 135, a, b) and the rods be raised to a horizontal position, the rubber is put on the stretch (c, d), so that when the rods are released they will be pulled downward by the elastic reaction of the rubber. This last demonstration has been held to indicate that during inspiration the interosseous portion of the internal intercostals is put on the stretch and in an oblique position, and therefore in a relation favorable for effective action during contraction. The ribs, however, differ essentially from such a model in the fact that they are curved bars, that their

ends are not free, and that the movement of rotation is materially different. In fact, the mechanical conditions are so complex that deductions from phenomena observed in such gross demonstrations or by means of geometric figures such as suggested by Rosenthal and others must be accepted with caution.

There is no doubt that stimulation of any of the intercostal fibres causes an elevation of the rib below if the rib above be fixed, and that if the excitation be sufficiently strong and the area be large, the effect may extend from rib to rib, and thus á large part of the thoracic cage will be elevated. Consequently, it has been assumed that, should the upper ribs be fixed, the contractions of both sets of intercostals would elevate the system of ribs below. But the experiments of Martin and Hartwell[1] show that during forced inspiration the internal intercostals contract alternately with the diaphragm and the external intercostals, and therefore are expiratory. Moreover, Ebner[2] has found, as a result of elaborate measurements, that the intercostal spaces, excepting the first two, are, instead of being narrowed, actually widened during inspiration.
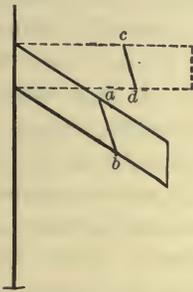
FIG. 134.—Model to illustrate the action of the external intercostals and interchondrals.
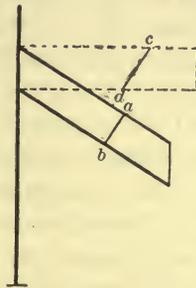
FIG. 135.—Model to illustrate the action of the interosseous portion of the internal intercostals.

An examination of the origins and insertions of the external intercostals and the interosseous portion of the internal intercostals, and of their actions during contraction, renders it apparent that it is possible for the externi to elevate the ribs and to widen the intercostal spaces, but that such effects are impossible in the case of the interosseous portion of the internal intercostals. Thus, if we take the model described above (Fig. 134), project a line a, b in imitation of the relation of the external intercostals to the ribs, and raise the parallel bars to a horizontal position, the distance between c, d is shorter than that between a, b. It is but a logical step from this demonstration to assume that, should a strip of muscle be placed between a, b, the muscle in *shortening* would pull the bars upward, at the same time widening the intercostal spaces. If now the upper ribs be fixed, it is obvious that the external intercostals must raise the ribs and open up the intercostal spaces during contraction. This same reasoning applies to the interchondrals, and the experiments of Hough[3] show that they contract synchronously with the diaphragm, and therefore with the external intercostals.

[1] *Journal of Physiology*, 1879–80, vol. 2, p. 24.   [2] *Loc. cit.*
[3] *Studies from the Biological Laboratory, Johns Hopkins University*, March, 1894.

In considering the interosseous portion of the internal intercostals we find that during the passive condition they are placed nearly at right angles to the ribs. If contraction takes place, it is obvious that the mechanical response must be an approximation of the ribs and a lessening of the width of the intercostal spaces. It must also be apparent that during the movement of inspiration these fibres are put on the stretch, which can be demonstrated in the above model. Thus, if we put a rubber band at right angles to the parallel rods (Fig. 135), we will find that when the rods are in the horizontal position, in imitation of the position of the ribs at the beginning of expiration, the distance between *c, d* is greater than that between *a, b ;* therefore if we lessen the distance between *c, d,* as when the muscle-fibres contract, the mechanical result of contraction must be approximation, the opposite to that which occurs during inspiration.

While the whole subject of the actions of the intercostal muscles must still be regarded as in an unsettled condition, yet there is no reasonable doubt that the externi and the intercartilaginei contract during inspiration, and the interosseous portion of the internal intercostals during expiration. Admitting this to be true, it is, however, by no means clear whether or not these muscles are for the purpose of altering the volume of the thorax. It is probable, as suggested by Landois, that their chief function is to maintain, during all phases of the respiratory movements, a proper degree of tension of the intercostal tissues. If this view be correct, the external intercostals and interchondrals contract during inspiration chiefly for the purpose of causing greater tension of the intercostal tissues, so as to counteract the influence of the increase of negative intrathoracic pressure; while during expiration, when their relaxation occurs, a substitution for this relaxation is provided by the contraction of the interosseous portion of the internal intercostals, so that the tension of the intercostal tissues is maintained. The internal intercostals must prove most effective during forced expiratory efforts—for example, in coughing, when the intercostal tissues are subjected to high positive intrathoracic pressure, and there is a consequent tendency to outward displacement, which is met and counteracted by the internal intercostals.

During forced inspiration the *scaleni* and the *serrati postici superiores* contract vigorously, so that the sternum and the first five ribs are elevated, thus raising the thoracic cage as a whole. At the same time the *serrati postici inferiores,* the *quadrati lumborum,* and the *sacro-lumbales* are active in pulling the lower ribs downward and backward. Besides these muscles there are a number of others which directly or indirectly affect the size of the thorax and which may be brought into activity ; chief among these are the *sterno-cleido-mastoidei,* the *trapezei,* the *pectorales minores,* the *pectorales majores* (costal portion), the *rhomboidei,* and the *erectores spinæ.*

The *sterno-cleido-mastoid* passes from the mastoid process and the superior curved line of the occipital bone to the upper front surface of the manubrium and the upper border of the inner third of the clavicle. These muscles elevate the upper part of the chest when the head and neck are fixed. The

trapezius passes from the occipital bone, the ligamentum nuchæ, the spines of the seventh cervical and of all the dorsal vertebræ, and the supraspinous ligament to the posterior border of the outer third of the clavicle, the inner border of the acromion process, the crest of the spine of the scapula, and to the tubercle near the root. The trapezei help to fix the shoulders. The *rhomboideus minor* passes from the ligamentum nuchæ and the spines of the seventh cervical and first dorsal vertebræ to the root of the spine of the scapula. The *rhomboideus major* passes from the spines of the first four or five dorsal vertebræ and the supraspinous ligament to the inferior angle of the scapula. The trapezei and rhomboidei fix the shoulders, affording a base of action from which the pectorales act. The *pectoralis major* passes from the pectoral ridge of the humerus to the inner half of the anterior surface of the clavicle, the corresponding half of the anterior surface of the sternum, the cartilages of the first six ribs, and the aponeurosis of the external oblique muscle. The *pectoralis minor* passes from the coracoid process of the scapula to the upper margin and outer surface of the third, fourth, and fifth ribs close to the cartilages and to the intercostal aponeuroses. The pectorales minores and the costal portion of the pectorales majores raise the ribs when the shoulders are fixed. The *erectores spinæ* are composite muscles extending along each side of the spinal column, each consisting of the sacro-lumbalis, the musculus accessorius, the cervicalis ascendens, the longissimus dorsi, the transversalis cervicis, the trachelo-mastoid, and the spinalis dorsi. The erectores spinæ straighten and extend the spine and the neck, and thus tend to raise the sternum, the costal cartilages, and the ribs. The *infrahyoidei* may also be included among the muscles engaged in forced inspiration, since they may aid in the elevation of the sternum.

Summary of the Actions of the Chief Muscles of Inspiration.—During *quiet inspiration* the *diaphragm* contracts, thus increasing the vertical diameter of the thorax, its effectiveness being augmented by the associated actions of the *quadrati lumborum* and the *serrati postici inferiores*, the former fixing the twelfth ribs, and the latter fixing the ninth, tenth, eleventh, and twelfth ribs, and thus preventing the muscular slips of the diaphragm attached to these ribs from drawing them inward and upward and thus diminishing the cavity of the thorax. Coincidently with the contractions of these muscles the *scaleni* fix the first and second ribs, and the *serrati postici superiores* aid in fixing the second ribs and elevate the third, fourth, and fifth ribs; the *intercostales externi et intercartilaginei* and the *levatores costarum longi et breves* elevate and evert the first to the tenth ribs, inclusive, throwing the lower end of the sternum forward; and the *levatores*, in conjunction with the *quadrati lumborum* and the *serrati postici inferiores*, aid in fixing the lower ribs and even draw them backward. The *intercostales externi* also serve to maintain a proper degree of tension of the intercostal tissues.

During *forced inspiration* the *scaleni* and the *serrati postici superiores* act more powerfully and thus raise the sternum with its attached costal cartilages and ribs, being assisted by the *sterno-cleido-mastoidei* and the *infrahyoidei* when the head and neck are fixed, and by the *pectorales majores et minores*

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when the shoulders are fixed by the *trapezei* and the *rhomboidei*.   The *erectores spinæ* further assist this action by extending the spinal column.

Movements of Expiration.—During quiet breathing expiration is effected mainly or solely by the passive return of the displaced parts.   Normal expiration is therefore essentially a passive act, although it may be assisted by the contraction of the interosseous portion of the internal intercostals.   The most important factors are unquestionably the elastic tension of the lungs, costal cartilages, intercostal spaces, and abdominal walls, together with the weight of the chest.

The lungs after quiet expiration are in a state of elastic tension equal to a pressure of $+1.9$ to $+3.9$ millimeters of mercury (see p. 505), which pressure during inspiration is increased in proportion to the depth of the movement. As soon, therefore, as the inspiratory muscles cease to contract, this tension comes into play, and, aided by elastic and mechanical reactions below noted, forces air from the lungs.   This elasticity, and the facility with which the air is expelled, may be demonstrated by inflating a pair of excised lungs and then suddenly allowing a free egress of the air: collapse occurs with remarkable rapidity, with a force proportionate to the degree of distention.   The elastic costal cartilages are similarly put on the stretch: the lower borders are drawn outward and upward and are thus twisted out of position, so that as soon as the inspiratory forces are withdrawn they must untwist themselves, further aiding the elastic reaction of the lungs.   The intercostal spaces, excepting the first two, are widened and the tissues are stretched, and the diaphragm during its descent presses upon the abdominal viscera, rendering the abdominal walls tense.   When, therefore, inspiration ceases the reaction of the tense and elastic intercostal tissues aids in bringing the chest into the position of rest, while the stretched abdominal walls press upon the abdominal viscera and thus force the diaphragm upward.   Finally, the chest-walls by their weight tend to fall from the position to which they have been raised, adding thus another factor toward the elastic reaction of the lungs, costal cartilages, intercostal tissues, and abdominal walls.

Whether or not the interosseous portion of the internal intercostal muscles assists in expiration cannot be stated with positiveness.   The fact that these muscles contract during the expiratory phase and that the contraction results in an approximation of the ribs leads to the belief that they are expiratory. But, as before stated (p. 512), this activity may be primarily for the purpose of maintaining a proper degree of tension of the intercostal tissues.   In the dog these muscles are not active until dyspnœa appears, while in the cat they do not come into play until extreme dyspnœa has set in (Martin and Hartwell). These facts certainly militate against regarding them as active expiratory factors during quiet breathing, while during forced expiration they may with accuracy be considered as being in part at least expiratory in function.   We are therefore justified in concluding that normal quiet expiration is essentially a passive act due to elastic reaction and to the mechanical replacement of displaced parts.

During forced expiration certain muscles may be active, the chief being the *intercostales interni interossei*, the *triangulares sterni*, the *musculi abdominales*, and the *levatores ani*. The *intercostales interni interossei* are probably active expiratory muscles during forced expiration, but they can prove effective only when the lower part of the thoracic cage is fixed or drawn down—an act which is accomplished chiefly by the abdominal muscles.

The *triangulares sterni* pass outward and upward from the lower part of the sternum, the inner surface of the ensiform cartilage, and the sternal ends of the costal cartilages of the two or three lower sternal ribs, to the lower and inner surfaces of the cartilages of the second to the sixth ribs, inclusive. They draw the attached costal cartilages downward during expiration.

The *abdominales* during quiet expiration are passive, and aid in the expulsion of air from the lungs simply by their elasticity; but during forced expiration, by contraction, they are active expiratory factors.

The *obliquus externus* arises by slips on the outer surface and lower borders of the lower eight ribs, and is inserted into the outer lip of the anterior half of the crest of the ilium and into the broad aponeurosis which blends with that of the opposite side in the linea alba. The *obliquus internus* passes from the outer half or two-thirds of Poupart's ligament, the anterior two-thirds of the middle lip of the crest of the ilium, and the posterior layer of the lumbar fascia to the cartilages of the last three ribs and the aponeurosis of the anterior part of the abdominal wall. The *rectus abdominis* passes from the crest of the pubes and the ligaments in front of the symphysis pubis to the cartilages of the fifth, sixth, and seventh ribs, and usually to the bone of the fifth rib. The *transversalis abdominis* passes from the outer third of Poupart's ligament, the anterior three-fourths of the inner lip of the iliac crest, by an aponeurosis from the transverse and spinous processes of the lumbar vertebræ, and from the inner surface of the sixth lower costal cartilages to the pubic crest and the linea alba. The fibres for the most part have a horizontal direction. The *pyramidalis* passes from the anterior surface of the pubes and the pubic ligament to the linea alba. It is obvious from the points of origin and insertion of the abdominal muscles that during contraction they co-operate toward diminishing the volume of the thorax in three ways: (1) By offering a base of action for the internal intercostals, and thus aiding in the approximation of the ribs; (2) by depressing and drawing inward the lower end of the sternum and the lower costal cartilages and ribs; (3) by forcing the abdominal viscera against the diaphragm, thrusting it upward. The abdominales are unquestionably the chief expiratory muscles.

The *levatores ani* converge from the pelvic wall to the inner part of the rectum and the prostate gland. They form the largest part of the muscular floor of the pelvic cavity. The levatores ani are important during forcible expiration by resisting the downward pressure of the pelvic viscera caused by the powerful contractions of the abdominal muscles, but they must be regarded rather as associated in the act of expiration, and not as true expiratory muscles.

Summary of the Actions of the Chief Muscles of Expiration.—During

quiet expiration no muscular factors are involved, unless it be the contraction of the *intercostales interni interossei*, in which event they are more probably engaged in maintaining the tension of the intercostal tissues than in actually diminishing the capacity of the thorax.

During *forced expiration* the *abdominales* flex the thorax upon the pelvis, force the abdominal viscera against the diaphragm, thrusting it upward, and by pulling upon the lower margins of the thoracic cage draw them inward and at the same time offer a base from which the *intercostales interni inter-ossei* act to pull the ribs downward; the *triangulares sterni* contract at the same time and pull downward the cartilages of the second to the sixth ribs, inclusive.

Associated Respiratory Movements.—Associated with the thoracic and abdominal movements of respiration are movements of the face, pharynx, and larynx. The nostrils are slightly dilated during inspiration and passively return to their condition of rest during expiration; the soft palate moves to and fro with the inflow and outflow of air, and the glottis is widened during inspiration and narrowed during expiration. During labored inspiration, besides the above movements, the mouth is usually opened; the muscles concerned in facial expression may be active, giving the individual an appearance of distress; the soft palate is raised, and the larynx descends. The widening of the nares and the glottis, the opening of the mouth, the elevation of the soft palate, and the descent of the larynx during inspiration are obviously for the purpose of lessening the resistance to the inflow of air.

Intrapulmonary or Respiratory Pressure and Intrathoracic Pressure. —The tidal flow of air to and from the lungs during the respiratory movements is due, as already stated, to the differences between the pressure within the lungs and that outside the body. During inspiration the enlargement of the thorax causes an expansion of the lungs and a consequent diminution of pressure within them, so the air is forced through the air-passages until the pressure within the lungs equals that of the atmosphere; during expiration there occur elastic and mechanical reactions whereby the pressure within the lungs is greater than that of the atmosphere, consequently air is expelled until an equilibrium is again established. It is apparent, then, that during inspiration there exists within the lungs a condition of *negative* pressure, and that during expiration the pressure is *positive*. If a manometer be so arranged as in no way to interfere with the ingress and egress of air, it will be found that during inspiration the column of mercury sinks, while during expiration it rises. Donders found by connecting a manometer with the nasal passage that the pressure during quiet inspiration was —1 millimeter of Hg, and during expiration +2 to 3 millimeters. Ewald gives as corresponding values —0.1 millimeter and +0.13 millimeter, and Mundhorst, —0.5 millimeter and +5 millimeters. During deep inspiration Donders noted a pressure of —30 millimeters, and when the mouth and nose were closed, —57 millimeters. During forced expiration, with respiratory passage closed, it was +87 millimeters; but these figures have been exceeded.

It will be observed that during quiet respiration intrapulmonary pressure (pressure *within* the lungs) oscillates between negative and positive and *vice versâ*, whereas intrathoracic pressure (pressure *outside* the lungs) is persistently negative, the amount by which it differs from atmospheric pressure becoming greater during inspiration and diminishing to the previous level during expiration (p. 505). Under forced expiration, however, when the air-passages are obstructed intrathoracic pressure may become positive. This may be demonstrated in this way: If a manometer be connected with the mediastinum of a cadaver, and the chest be pulled upward in imitation of deep inspiration, intrathoracic pressure will be found to be about −30 millimeters. If now a second manometer be connected with the trachea, and air be forced into the lungs through a tracheal tube, as intrapulmonary pressure rises intrathoracic pressure falls, so that when the former reaches +30 millimeters the intrathoracic negative pressure exerted by the elastic traction of the lungs is counterbalanced and the pressure within and outside the lungs is equal. If intrapulmonary pressure now rise above this limit, intrathoracic pressure must proportionately become positive. During violent coughing, when the expiratory blast is obstructed and the muscular effort is powerful, intrapulmonary pressure may rise to +80 millimeters or more.

The intercostal tissues tend to be drawn inward as long as negative intrathoracic pressure exists, and to be forced outward when there is positive intrathoracic pressure; hence during inspiration the traction becomes more marked with the rise of intrathoracic pressure, and during expiration the reverse; while during forced expiration with obstructed air-passages the pressure exerted by the effort of the expiratory muscles, together with the weight of the chest and the elastic reaction of the costal cartilages, etc., may be, as above stated, far more than sufficient to counterbalance the traction exerted by the distended elastic lungs, and thus cause positive intrathoracic pressure.

The influences exerted by changes in intrathoracic and intrapulmonary pressure upon the circulation are marked and important, and may be so pronounced as to cause an obliteration of the pulse.

Respiratory Sounds.—During the respiratory acts characteristic sounds are heard in the lungs. A study of these sounds, however, properly belongs to physical diagnosis.

The Value of Nasal Breathing.—Nasal breathing has a value above breathing through the mouth, inasmuch as the air is warmed and moistened and thus rendered more acceptable to the lungs, more or less of the foreign particles in the air are removed, and noxious odors may be detected.

B. The Gases in the Lungs, Blood, and Tissues.

Alterations in the Gases in the Lungs.—The object of respiratory movements is to renew the air within the lungs, which air is constantly being vitiated, and thus supply O and remove CO_2 and other effete substances. The lungs of the average adult man after quiet expiration contain about 2800 cubic centimeters (170 cubic inches) of air. During quiet respiration there is an

inflow and outflow of about 500 cubic centimeters (30 cubic inches), therefore from one-sixth to one-fifth of the air in the lungs is renewed by each act. Since the respirations occur at so frequent a rate as 16 to 20 per minute, it seems apparent that there must be a rapid loss of O and a gain of CO_2. This is proven by analyses of inspired and expired air. Inspired air is under normal circumstances atmospheric air, composed of oxygen, nitrogen, argon, and carbon dioxide, with more or less moisture, traces of ammonia and nitric acid, dust and micro-organisms, etc. The essential differences between inspired and expired air are shown by the following table, the figures for the gases being in volumes per cent. Argon constitutes about 1 per cent. of the nitrogen as given in the table:

	O	CO_2	N	Watery Vapor.	Temperature.	Volume (Actual).
Inspired air .	20.81	0.04	79.15	Variable.	Average, about 20°	
Expired air .	16.03	4.38	79.30	Saturated.	Average, about 36.3°	Diminished
	4.78	4.34	0.15			2 to 2½ %.

Expired air is therefore 4.78 volumes per cent. poorer in O, 4.34 volumes per cent. richer in CO_2, and 0.15 volume per cent. richer in N; it is saturated with watery vapor, and is of higher temperature and of less actual volume. In addition, expired air contains various effete bodies, such as organic matter ("crowd-poison"), hydrogen, marsh-gas, etc.

The relative quantities of O absorbed and of CO_2 given off are not constant, and the ratio is known as the *respiratory quotient*. This is obtained by dividing the volume of CO_2 given off by that of O absorbed, $\dfrac{CO_2,\ 4.34}{O,\ 4.78} = 0.908$. Hence, for each volume of O that is lost 0.908 volume of CO_2 is gained. Various circumstances affect the quotient (p. 544). The quantity of N given off is about 7 grams per diem.

The quantity of watery vapor lost by the lungs varies inversely with the amount contained in the atmosphere and with the volume of air respired. The less the moisture in the atmospheric air and the larger the volume of air respired, the greater the loss. Valentine, in experiments on eight young men, records a daily loss varying from 349.9 to 773.3 grams, or an average of 540 grams. Vierordt records a loss of 330 grams, while Aschenbrandt estimates a daily loss of 526 grams.

The temperature of the expired air varies with the temperature and volume of the inspired air and with the temperature of the body. Valentine and Bruner found that when the temperature of inspired air was from 15° to 20°, that of expired air was 37.3°; when that of inspired air was —6.3°, expired air had a temperature of 29.8°; while when the inspired air was at 41.9°, that of expired air was 38.1°. When the air is respired through the nose the expired air is warmer than when respiration occurs through the mouth. Bloch[1]

[1] *Zeitschrift für Ohrenheilkunde*, 1888, vol. xviii. p. 215.

records a difference of 1.5° to 2°. The figures by other observers vary from 0.5° to 1.5°. The larger the volume of air respired, other things being equal, the less the increase of temperature.

The volume of expired air is from 10 to 12 per cent. greater than that of inspired air, this increase being due to expansion caused by the increase of temperature. When proper deductions are made for temperature and barometric pressure, the actual or corrected volume is less by 2 to $2\frac{1}{2}$ per cent.

Lossen estimated that 0.0204 gram of ammonia is eliminated per diem in the expired air, but Voit's investigations indicate that expired air usually does not contain even a trace of ammonia.

Alterations in the Gases in the Blood.—The blood in the pulmonary artery is of the typical venous color—that is, deep bluish-red. During its passage through the lungs it becomes scarlet-red, or, commonly speaking, arterialized or aërated. If we take arterial blood and deprive it of oxygen, the color changes to a venous hue; if now we shake the bluish-red blood in air or O, the scarlet-red color is restored. We have here the suggestion that the blood while passing the lungs absorbs O. Analyses show that not only does absorption of O occur, but that there is simultaneously with this an elimination from the blood of CO_2.

Arterial and venous blood each contains approximately 60 per cent. volumes of O and CO_2; that is, for about every 100 volumes of blood 60 volumes of gas will be obtained. Such analyses demonstrate also that while the total volumes per cent. of O and CO_2 are about the same, the proportions are different. The following table, after Ellenberger,[1] gives the volumes per cent. of gases in the arterial blood of various animals:

Animal.	Total.	O.	CO_2.	N.
Dog	57.9	19.8	37.0	1.9
Cat	43.2	13.1	28.8	1.3
Sheep	57.6	10.7	45.1	1.8
Rabbit	49.3	13.2	34.0	2.1
Man	63.5	21.6	40.3	1.6
Fowl	58.8	10.7	48.1	

Pflüger obtained as averages of analyses of arterial blood of dogs 58.3 volumes per cent., consisting of 22.2 volumes per cent. of O, 34.3 volumes per cent. of CO_2, and 1.8 volumes per cent. of N. Venous blood, according to estimates by Zuntz based on a large number of analyses, contains 7.15 volumes per cent. less of O and 8.2 volumes per cent. more of CO_2. The quantity of N is practically the same in both arterial and venous blood.

The proportions of O and CO_2 in arterial blood vary but little in specimens taken at random from the arterial system, while those of venous blood, on the contrary, differ considerably according to the locality of the vessel as well as to the degree of activity of the structures whence the blood comes. Thus, venous blood from an active secreting gland differs very little in its composition, gaseous and otherwise, from typical arterial blood, whereas when

[1] *Physiologie der Haussäugethiere*, 1890, vol. i. p. 204.

the gland is inactive the blood is distinctly venous. The arterial character of the venous blood in the former case is due to the considerable increase in the quantity of blood passing through the gland during activity, the result being that the loss and gain of substances are not so noticeable, although the total quantities of O and CO_2 exchanged are actually greater than when the gland is at rest and the blood coming from it has the typical venous characters.

The venous blood during its passage through the lungs acquires O and loses CO_2. After the blood is arterialized it passes from the lungs into the left side of the heart, from which it is forced to the aorta and its ramifications and ultimately into the capillaries. Here it undergoes a retrograde change, parting with some of its O and taking in exchange CO_2; consequently the gaseous interchange between the blood and the tissues is the reverse of that occurring between the blood and the air. Thus we find that the interchange of O and CO_2 occurs in a distinct series of events: (1) Oxygen is carried as a constituent of the atmospheric air to the alveoli; (2) here it is absorbed by the venous blood, which at the same time gives off CO_2 to the air in the alveoli; (3) O is now in major part conveyed to the tissues, in which it is taken up and utilized in processes of oxidation, CO_2 being the chief effete product, which is formed immediately or ultimately and given to the blood (a part of the O is consumed by the blood, CO_2 being one of the results); (4) the venous blood is now conveyed to the lungs, CO_2 is given off and O is received in exchange, and the series of events is repeated.

The Forces Concerned in the Diffusion of O and CO_2 in the Lungs.— If the air expired be collected in a number of parts, each successive portion will be found to contain a smaller percentage of O and a larger percentage of CO_2. The air in the beginning of the respiratory tract (nose and mouth) varies from atmospheric air but little in composition, while that in the alveoli contains considerably less O and much more CO_2. With each quiet act of inspiration the quantity of air breathed is from three to four times greater than the capacity of the trachea and bronchi, so that with each respiratory act two-thirds or more of the fresh air is carried into the alveoli. When expiration occurs a similar volume of the vitiated air within the alveoli is driven into the bronchi and trachea, and thus a certain percentage is expelled from the body. Thus the mere volume and force of the air-currents must obviously be of great value in equalizing the composition of the air in the different parts of the respiratory tract.

The contractions of the heart exert similar mechanical influences. With each contraction intrathoracic pressure is lessened, so that there is a slight expansion of the lungs, just as would be caused had the thorax been slightly enlarged, and consequently there is a movement of air toward and into the alveoli. During diastole intrathoracic pressure returns to the previous level, the volume of the lungs is diminished, and the air is driven from the alveoli. Thus each heart-beat causes a to-and-fro movement of the air. These oscillations, which are termed *cardio-pneumatic movements*, are of more importance than might seem at first sight, for it has been shown that in cases of suspended

animation and in hybernating animals they aid materially in pulmonary ventilation.

Besides these mechanical factors there is present the important factor of the diffusion of gases, O diffusing toward the alveoli and CO_2 toward the anterior nares. The rapidity with which diffusion occurs, other things being equal, depends upon the differences in the "partial pressure" of the gas at various regions. Each gas forming part of a mechanical mixture exerts a partial pressure proportional to its percentage of the mixture. Thus, atmospheric air contains 20.81 volumes per cent. of O, 0.04 volumes per cent. of CO_2, and 79.15 volumes per cent. of N. If the air exists at 760 millimeters barometric pressure, each gas will exert a *part* of the total pressure, or a "partial pressure," equivalent to its respective volume. Should we wish to find the partial pressure of O, it may be ascertained simply by taking $\frac{20.81}{100}$ of the total pressure $= \frac{20.81 \times 760}{100}$ $= 158.15$ millimeters; similarly, the partial pressure of CO_2 would be $\frac{0.04 \times 760}{100} = 0.30$ millimeter; and that of N, $\frac{79.15 \times 760}{100} = 601.54$ millimeters. Knowing, then, the composition of any mixture of gases and the total pressure under which it exists, it is a matter of very simple calculation to determine the partial pressure of each of the various gases constituting the atmosphere. Expired air is poorer in O and richer in CO_2 than inspired air, and alveolar air is altered even to a greater extent than expired air; hence the partial pressures must be affected similarly.

The first portion of the air expired contains a maximum amount of inspired air and a minimum amount of the air contained in the air-passages previous to the inspiratory act; but as expiration continues the mixture becomes poorer and poorer in inspired air and similarly richer in the vitiated air from the smaller air-passages and the alveoli; in fact, the last portion of expired air is very similar to, if not identical in its composition with, that in the alveoli. The following partial pressures of O and CO_2 in inspired air and alveolar air indicate the extent to which the composition varies in different parts of the respiratory tract:

Gas.	Inspired Air.	Alveolar Air.
O	158.15 millimeters.	122 millimeters.[1]
CO_2	0.30 millimeter.	38 millimeters.

Since the partial pressure of O in inspired air is about 158.15 millimeters, and as it is but about 122 millimeters in the alveoli, and as the air is poorer in O as we pass from the nares to the alveoli, it is obvious that a force must be exerted constantly to cause a diffusion of O from the larger air-passages to the bronchioles and from the bronchioles to the alveoli—that the O must diffuse from the region of highest pressure to that of lowest pressure. During life an equilibrium can never be established, because of the constant supply of fresh air and the continual passage of O from the alveoli to the blood. The

[1] The exact per cent. composition of alveolar air is not known; these figures are estimates.

same relations of partial pressure are observed in connection with CO_2, except that the air in the alveoli is incessantly acquiring this gas from the blood, causing the per cent. composition of CO_2 to be much in excess of that found in the atmosphere. The partial pressure of CO_2 in the alveolar air is about 38.00 millimeters, while in inspired air it is only 0.30 millimeter; hence CO_2 must diffuse from the alveoli outward.

There are, therefore, three important factors concerned in the admixture and purification of the air in the lungs: (1) The tidal movements caused by inspiration and expiration, which movements by the mere force of air-currents cause a partial mixture of the air; (2) the smaller wave-movements (cardio-pneumatic) produced by the heart-beats, and similar in effect to, but much less effective than, the first; (3) the diffusion of O and CO_2, depending upon differences in their partial pressures in the various parts of the respiratory tract.

The Forces Concerned in the Interchange of O and CO_2 between the Alveoli and the Blood.—The gases in the lungs are in the form of a mechanical mixture, while in the blood they are in solution or in chemical combination; hence we now have to deal with conditions quite different, involving the consideration of the relations of gases to liquids—a relationship of twofold nature, inasmuch as the gas may be found not only in solution, but in chemical association.

When an atmosphere consisting of O, CO_2, and N is brought in contact with water, each gas is absorbed independently not only of the others, but of the nature and quantity of all other gases which may happen to be in solution. The quantity of each gas dissolved depends upon its relative solubility as well as upon the temperature and the barometric pressure. The coefficient of absorption of any fluid is the quantity of gas dissolved at a given temperature and pressure, and is in inverse relation to temperature and in direct relation to pressure. The following absorption-coefficients of water for O, CO_2, and N at 760 millimeters of Hg have been obtained by Winkler:[1]

Temperature.	O.	CO_2.	N.
0°	0.04890	1.7967	0.02348
15°	0.03415	1.0020	0.01682
40°	0.02306	. .	0.01183

Thus, at 0° C and 760 millimeters pressure each volume of water absorbs 0.0489 volume of O; at 15°, 0.03415 volume; and at 40°, 0.02306 volume. The absorption-coefficient falls, it will be observed, with the increase of temperature. Comparing the solubilities of the three gases, it will be seen that at the same temperature and pressure a considerably larger quantity of CO_2 is absorbed than of O—nearly four times more—whereas the quantity of N absorbed is less than one-half as much as that of O.

The quantity of a gas absorbed by a given liquid at a given temperature is proportionate to its coefficient of solubility and to the pressure, and is the same whether the gas exist free or as a constituent of a complex atmosphere, pro-

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[1] *Zeitschrift für physikalische Chemie*, 1892, vol. 9, p. 173.

vided that the pressure exerted by the gas in both cases be the same. Thus, atmospheric air consists of 20.81 volumes per cent. of O, 0.04 volume per cent. of CO_2, and 79.15 volumes per cent. of N. Each gas exerts a partial pressure in proportion to its percentage of the mixture. Assuming that the air is at standard atmospheric pressure, the partial pressure of O is 20.81 per cent. of 760 millimeters of Hg, or 158.15 millimeters. The quantity of O absorbed from the air at 0° C and 760 millimeters pressure is therefore the same as when the atmosphere consists of pure O at a pressure of 158.15 millimeters. The absorption-coefficient must consequently be $\dfrac{20.81 \times 0.0489}{100} = 0.01$ volume. Therefore 100 volumes of water at 0° C. and 760 millimeters pressure absorb from the air 1 volume of O.

If the partial pressure of O be increased or decreased, the quantity absorbed will rise or fall accordingly. From this it is obvious that O must exist under a certain degree of pressure to prevent its passing out of solution, which is expressed by the term *tension* of solution, meaning, in a word, the pressure required to keep the gas in solution. If the partial pressure of the gas diminishes, the gas in solution is given off until the *partial pressure* of the gas in the *air* and the *tension* of the gas in *solution* are equal. Conversely, as the partial pressure of the gas in the air increases, the gas in solution will be under correspondingly higher tension.

Tension of O.—The absorption-coefficient of blood for O is nearly the same as that of water, so that blood at 0° should absorb from the atmosphere about 1 volume per cent. of O, but less than one-half as much at the temperature of the body. The results of experiments show, however, that blood contains considerably more than this, the average for arterial blood being 22.2 volumes per cent., or very much more than can be accounted for by the laws of partial pressures and tensions. Moreover, when the blood is subjected to a vacuum pump there is evolved a small amount of gas consistent with the diminution of pressure, but the great bulk of it does not come off until the pressure has been reduced to $\frac{1}{30}$ to $\frac{1}{10}$ of an atmosphere. Finally, the quantity absorbed is affected but little by changes in pressure above a certain standard. These facts indicate that almost all of the O must be in chemical combination, the combination being with hæmoglobin in the form of oxyhæmoglobin. This chemical union is readily dissociated at a constant minimal pressure which is termed the *tension of dissociation*. There is a persistent tendency of the gas in such a compound to become disengaged, so that when oxyhæmoglobin is placed under circumstances where the tension or the partial pressure of O is less than that in the compound, dissociation occurs; conversely, when hæmoglobin is brought in contact with O at a pressure above the minimal constant of dissociation ($\frac{1}{30}$ to $\frac{1}{10}$ of an atmosphere), the two unite to form oxyhæmoglobin. One gram of hæmoglobin combines, according to Hüfner,[1] with 1.59 cubic centimeters of O at 0° and 760 millimeters pressure. Assuming that 100 volumes of blood contain 15 grams of hæmoglobin (p. 335), if oxidized into oxyhæmoglobin the

[1] *Zeitschrift für physiologische Chemie,* 1877–78, vol. ii. p. 389.

quantity of gas combined with the hæmoglobin would be equal to 23.38 volumes per cent. of the blood; in other words, arterial blood should contain 23.38 volumes per cent. of O. This, however, is more than is found, but the deficit is accounted for by the fact that only from $\frac{9}{10}$ (Pflüger) to $\frac{14}{15}$ (Hüfner) of the hæmoglobin is saturated.

The plasma and the serum absorb but very small quantities of O—according to Pflüger, only 0.26 volume per cent. Owing to the relatively low absorption-coefficient of the plasma compared with the O-capacity of the hæmoglobin, as well as to the fact that the hæmoglobin is practically saturated at a relatively low pressure, the quantity of O absorbed is not materially affected by an increase of pressure above the level of the tension of dissociation; the slight increase which does occur is due chiefly to absorption by the plasma.

The tension of O in arterial and venous blood must be ascertained separately, inasmuch as each contains a different percentage. Following this method, Strassburg[1] records the following averages: Arterial blood, 29.64 millimeters of Hg, or 3.9 per cent. of an atmosphere; and venous blood, 22.04 millimeters, or 2.9 per cent. of an atmosphere.

Tension of CO_2.—Venous blood contains about 45 volumes per cent. of CO_2. The results of experiments prove that only about 5 per cent. of this CO_2 is in simple solution, that from 10 to 20 per cent. is in firm chemical combination, and that from 75 to 85 per cent. is in loose combination.

When the blood at the temperature of the body is subjected to a vacuum, all of the CO_2 is given off; but if the blood-corpuscles be removed and the plasma and corpuscles each in turn be submitted to the pump, both will give off CO_2, the plasma yielding a larger volume than the corpuscles, but not so much as when they are together. Plasma and serum *in vacuo* give off only a portion of their CO_2; the remainder may, however, be dissociated by adding acid or red corpuscles. The red corpuscles therefore act as an acid and cause the disengagement of all the gas from the plasma; consequently, not only do the corpuscles yield up the CO_2 contained in them, but they are also active agents in bringing about the dissociation of CO_2 which is in chemical combination in the plasma. The dissociation is due in part, perhaps, to the presence of phosphates in the stromata of the red corpuscles, and to certain proteids, but the observations of Preyer and Hoppe-Seyler lead to the conviction that it is due chiefly to oxyhæmoglobin and hæmoglobin. Phosphates, proteids, hæmoglobin, and oxyhæmoglobin all have the power of expelling CO_2 from sodium carbonate in solution *in vacuo*, but this fact leaves us none the wiser as to which, if any, is active in this way in the blood. Arterial blood gives off its CO_2 more readily than venous blood.

Of the total quantity of CO_2, about 5 per cent. is in simple solution and from 10 to 20 per cent. is in firm chemical combination in the plasma, the latter requiring the addition of acid or of hæmoglobin, etc. to cause its dissociation *in vacuo*; while the remainder, constituting much the larger proportion, is in loose chemical union in both the plasma and the corpuscles. That which is in

chemical combination in the plasma is probably in part combined with globulin and alkali, and in part with sodium as carbonate and bicarbonate, the proportion of each varying with the tension of the CO_2. The white blood-corpuscles, so far as they contain any of the CO_2, hold it probably in combination with globulin and alkali and as carbonates of sodium. The great bulk of the gas disengaged from the corpuscles is derived from the red cells, but in what combination or combinations it exists is not positively known. The experiments of Setschenow, Zuntz, Bohr,[1] and others indicate that it is associated in some obscure way with hæmoglobin, and probably with a third body, such as globulin or alkaline phosphates; and yet hæmoglobin seems to have the power to hold the CO_2 in the absence of a third body. This latter fact has been shown by the experiments of Bohr, who compared the quantities of CO_2 absorbed by pure water and by solutions of pure crystallized hæmoglobin at constant temperature and varied pressure. He found that the weight of CO_2 absorbed by the water increased regularly with the increase of pressure, whereas the quantity absorbed by the solution of hæmoglobin was very large relatively to the lower pressures and small for higher pressures, and that the increments of absorption were in decreasing ratio to the rise of pressure. The absorption curve is therefore steep at first, becoming less and less so with the increase of pressure, and entirely different from the absorption line for pure water, which is straight. Moreover, the quantity of CO_2 dissolved was considerably in excess of that which physical laws could admit. The CO_2, in whatever form or forms it may exist in the red corpuscles, is in looser combination than in serum.

Strassburg's experiments show that the average tension of CO_2 in arterial blood is 21.28 millimeters of Hg, or 2.8 per cent. of an atmosphere, and in venous blood 41.04 millimeters, or 5.4 per cent. of an atmosphere.

Tension of N.—The quantity of nitrogen in the blood is about 1.8 volumes per cent. It is in simple solution in the blood-plasma, and the quantity in both venous and arterial blood is practically the same. Its presence and quantity are not of physiological importance.

The Interchange of O and CO_2 between the Alveoli and the Blood.— Let us now inquire into the factors which bring about the passage of O from the alveoli to the blood and of CO_2 from the blood to the alveoli. If we have two mixtures of the same gases, but in unlike proportions, and separate them by means of an animal membrane, diffusion will occur through the membrane until the partial pressures of the two gases are the same on the two sides of the membrane. Now modify this experiment by bringing an atmosphere of air in contact with water containing O, CO_2, and N in solution or in chemical combination: if the partial pressure of O in the air be greater than the tension of O in the water, O will pass to the water; if the partial pressure of CO_2 in the air be less than the tension of CO_2 in the water, CO_2 will pass to the air. If now we interpose an animal membrane between the atmosphere and the

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[1] *Exper. Untersuch. u. d. Sauerstoffaufnahme d. Blutfarbstoffes,* Kopenhagen, 1885; *Beiträge zur Physiologie,* Festschr. f. C. Ludwig, 1887, pp. 164–172.

water, the interchange of gases will continue as before. In this case we have conditions analogous to those which exist in the living organism: In the alveoli there is an atmosphere consisting of O, CO_2, and N; each gas is under a partial pressure proportional to its volume per cent. of the mixture; the pulmonary membrane and the walls of the capillaries may be regarded as a simple animal membrane separating the air in the alveoli from the blood; finally, the blood contains O, CO_2, and N, each of which is in a definite and independent degree of tension. Whether or not any or all of these gases will pass in one direction or the other must obviously depend upon the conditions of partial pressure and tension of each gas on the two sides of the membrane. The tension of O in venous blood, as above stated, is 22.04 millimeters of Hg, and of CO_2, 41.04 millimeters. What are the partial pressures of these gases in the alveoli? The precise pressures are not known, but it is estimated that the partial pressure of O is about 122 millimeters, and of CO_2 about 38 millimeters.

Comparing the partial pressures and the tensions of these two gases in the alveoli and the blood respectively, it is obvious that the conditions on the two sides of the membrane are favorable to the diffusion of O and CO_2, and in definite but opposite directions. This is illustrated in the following diagrammatic presentation:

	O.	CO_2.
Tensions in alveolar air	122.00	38.00
Pulmonary membrane		
Tensions in venous blood	22.04	41.04

Since the gases diffuse from the point of higher pressure or tension to that of lower pressure or tension, O passes from the alveoli to the blood, while CO_2 passes from the blood to the alveoli.

It is, however, impossible under certain circumstances to account for the transmission of all of either the O or the CO_2 by the laws of diffusion. In regard to O, physical forces are active to the extent that they cause a diffusion of O to the blood-plasma, where it is brought in contact with the hæmoglobin of the blood-corpuscles. The chemical union of O with hæmoglobin takes place at a low tension, hence the quantity of O taken up by the blood does not vary materially with the amount of O in the air breathed, no more O being taken up when pure O is respired than from atmospheric air, in which O constitutes only about 20 volumes per cent.; and Fränkel and Geppert record that the quantity of O in arterial blood is but little diminished even when the air-pressure is reduced as low as 378–365 millimeters. But Bohr found in experiments on dogs that the tension of O in arterial blood may even be higher than its partial pressure in the alveolar air; and Pflüger long since determined that when animals breathe pure N or H, no O passes from the blood into the alveoli. It is apparent from these latter facts that the transmission of O may not be entirely a matter of diffusion. In addition to the physical and chemical factors, it is possible, as suggested by Bohr, that the pulmonary tissue takes an active part as a specific secretory membrane in this transmission.

The problem in connection with CO_2 is also complex. It is commonly

believed that the passage of CO_2 from the blood to the alveoli is determined simply by the laws of diffusion, but Bohr[1] has found in experiments in which analyses of the blood and alveolar air were made simultaneously that the partial pressure of CO_2 in the alveolar air may be less than the average tension in the blood. Moreover, Bohr found in a series of experiments that even when the quantity of CO_2 in the atmosphere in contact with the blood was very small, but little more CO_2 diffused from the blood. Facts of this kind are explicable on the hypothesis that the pulmonary membrane is, as contended by Ludwig, Bohr, and others, actively engaged in the process, playing a specific excretory rôle, but our knowledge is as yet too incomplete to require the acceptance of such an hypothesis. Under ordinary conditions the tension of CO_2 in the alveoli is less than in the blood, and the transmission of CO_2 from the blood to air-cells may be explained satisfactorily by the laws of diffusion.

The Forces Concerned in the Interchange of O and CO_2 between the Blood and the Tissues.—Innumerable facts show that the chief seat of the chemical processes in the body is in the tissues, and that the decompositions are essentially of an oxidizing character whereby CO_2 is formed as one of the most important effete products; consequently the blood as it is carried through the capillaries gives up O and receives CO_2.

Experiments show that the tissues exert a strong reducing action, and that their avidity for O is so great that they will take it up at extremely low pressures. Moreover, never more than mere traces of O can be obtained from the tissues, because the gas upon its absorption immediately enters into chemical combination.

The tension of CO_2 in the tissues is considerably higher than in blood. Strassburg,[2] in a loop of intestine into which he injected atmospheric air, found that the tension was 58.52 millimeters of Hg, which is considerably greater than in either arterial or venous blood. Thus we find that the tension of O in the tissues is *nil*, owing to their greediness for this gas, while that of CO_2 is very high. Comparing the tensions of these two gases in the blood and the tissues, it will be observed that there are present conditions which are highly favorable to the passage of O to the tissues and of CO_2 in the reverse direction :

	O.	CO_2.
Tensions in arterial blood	29.64	21.28
Blood-vessel walls		
Tensions in tissues	0.00	58.25

It is manifest from the above that O should pass from the blood to the tissues, and CO_2 from the tissues to the blood.

The lymph is probably merely a passive medium in this interchange. It contains, according to Hammarsten, only traces of O, from 37.5 to 47.1 volumes per cent. of CO_2, and from 1.1 to 1.63 volumes per cent. of N. The mean percentage of CO_2 is lower than in serum, but Gaule has shown that the tension is higher. Doubtless the same relations hold good for the plasma and

[1] *Loc. cit.*   [2] *Loc. cit.*

the blood, so that, notwithstanding a smaller volume per cent. of CO_2 in the lymph, CO_2 passes to the blood because of the higher tension in the lymph.

Extraction of Gases from the Blood.—We have found that in the blood both O and CO_2 exist partly in solution and partly in chemical combination. The portion in solution comes off regularly with a diminution of pressure, but that which is in chemical combination remains so until the pressure is reduced to the level of the tension of dissociation. Since there are several of these combinations, such as O in oxyhæmoglobin and CO_2 in carbonates, bicarbonates, alkali phosphates, etc., portions of each of these gases come off at different pressures in accordance with their different tensions in the several chemical combinations. The portions in solution may be removed by the use of an ordinary air-pump, but those in chemical combination are held so firmly that the more powerful mercurial pump is required. A convenient pump of this kind has been devised by Dr. Geo. T. Kemp, the description of which he gives as follows :

FIG. 136.—Kemp's gas pump.

" To use the pump the reservoir bulb *Bb* (Fig. 136), the bulb *I*, the cylinder *SR* and *S'R'*, and the vessel *P* are filled with mercury. When the bulb *Bb* is raised the mercury rises in the tube *AC* and fills *B*, driving the air out by the path *FHOP*, the stopcock *Q* being closed. When *Bb* is lowered again the mercury flows back from *B* into *Bb*, creating a Torricellian vacuum in *B*. As soon as the mercury has fallen below the joint *D*, this vacuum in *B* becomes connected by the path *DEG* with the tubes *TGUG'T'* and the tube *VWYX*, and thence, when the stopcock is open, with the vessel to be exhausted. The air in this then diffuses to fill the vacuum in *B*, and becomes rarefied, so that the mercury rises from the cylinders *SR* and *S'R'* in the outer tubes *TG* and *T'G'*. The small inner tubes *RG* and *R'G'* are made so high that even when there is a complete vacuum in the outer tubes *TG* and *T'G'* the mercury will not rise high enough to cover them.
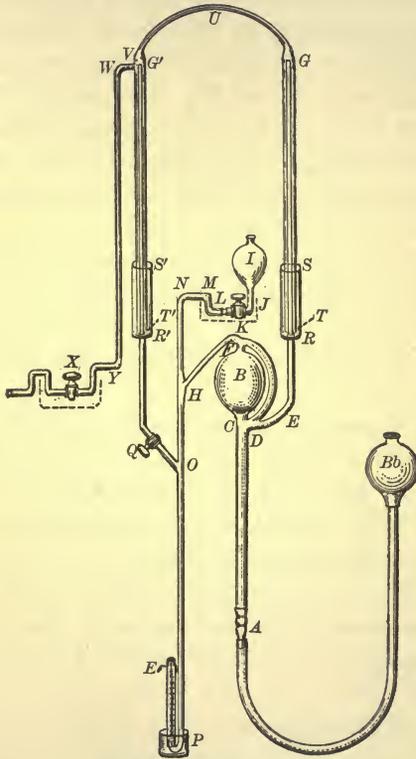
" On raising *Bb* again the mercury rises in *AC*, and as soon as the joint *D* is covered, all the air which has been caught in *B* is forced out by the path *FHOP*. Each time the bulb *Bb* is raised and lowered a certain amount of air is ex-

tracted from the receiver, until finally a vacuum is produced. In a similar way, when the receiver connected with the pump at Z contains any gas which we wish to analyze—as, for example, the gases given off by the blood in a vacuum—we put a eudiometer (Eu) over the bend of the tube at P, which, of course, is always under the mercury, and collect the gases as they are forced out.

"The extraction of the last traces of gas by raising and lowering Bb is a very tedious and laborious process, so that the final extraction of the gases can best be accomplished by the Sprengel pump $IJKLMNHOP$. The bulb and stopcock IJK are made separate, as shown in the figure, and are connected with LMN by a piece of rubber tubing, the whole being under mercury. This is accomplished by the bend $JKLM$, which is made so as to allow a narrow wooden box filled with the mercury to be slipped up over the bend high enough to cover the stopcock and thus prevent leakage of air. The same arrangement is shown at X, and is indicated by a dotted line in each instance. When the stopcock K is opened the mercury flows in, drops down the tube $NHOP$, and extracts the gases at H in the well-known manner of the Sprengel pump. The large bulb is for rapid exhaustion down to the last few millimeters of pressure, the rest being accomplished more slowly but more perfectly by the Sprengel. In extracting blood-gases the oxygen is given off suddenly and the CO_2 slowly. The great desideratum is to keep the tension of the gases in the blood-chamber down as near zero as possible—certainly below 20 millimeters of Hg. This is readily done with the large bulb when the O is evolved, while the Sprengel is able to remove the CO_2 as it is given off, thus obviating the continued raising and lowering of the reservoir bulb."

The gases collected are driven through the tube P into a eudiometer previously filled with mercury and inverted. The eudiometer (Fig. 137) is a calibrated tube in which the gases are measured. In the upper part of it are two platinum wires by means of which an electric spark is brought in contact with the gases. Hydrogen is introduced into the eudiometer in definite quantity (more than sufficient to combine with all of the O to form H_2O), and a spark is generated between the ends of the platinum wires, causing the O and the H to combine. The diminution in volume is now noted, one-third of which diminution is equal to the total volume of O obtained from the sample of blood. The quantity of CO_2 may be estimated by introducing into the eudiometer a piece of moistened fused potassium hydrate, which absorbs the CO_2, forming potassium carbonate. The loss in volume is the volume of CO_2 obtained from the blood. The residual gas consists of N and H, the latter being the excess not combined with O. The total quantity of H introduced being known, and also the quantity which combined with O, the difference is deducted from the volume N and H, the remainder being the volume N. Accurate analysis necessitates corrections for temperature, for

FIG. 137.—Eudiometer.

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tension of aqueous vapor, and for atmospheric pressure, as well as attention to the many details connected with gas-analysis.

Cutaneous Respiration.—In frogs the skin is a more important respiratory organ than the lungs, as is illustrated by the fact that asphyxia is more rapidly produced by dipping the animal in oil, and thus preventing the interchange of O and CO_2 through the skin, than by ligature of the trachea; moreover, the investigations of Regnault and Reiset show that in these animals nearly the same quantities of O are absorbed and CO_2 eliminated after the lungs are excised as in the intact animal. In man the reverse is the case, the cutaneous interchange being insignificant as compared with that in the lungs.

The quantity of CO_2 exhaled through the skin during twenty-four hours has been estimated by different observers from 2.23 grams to as much as 32.08 grams. Compared with pulmonary interchange, the ratio of O absorbed is probably about 1 : 100–200, and of CO_2 eliminated, 1 : 200–250.

Cutaneous respiration is, as a rule, subject to the same circumstances that affect the interchange in the lungs, and is accomplished, moreover, in the same way. In some instances, however, it is influenced in the opposite direction; for instance, it is increased by circumstances that hinder pulmonary respiration. Cutaneous respiration is favored by moist skin, and Ronchi found that it was increased by higher external temperature.

Internal or Tissue-respiration.—The main object of the respiratory mechanism is to supply the organism with O and to remove the CO_2 resulting from tissue-activity. The organism may be regarded as an aggregation of living cells, each of which during life consumes O and gives off CO_2. Activity depends essentially upon processes of oxidation; consequently, not only is oxidation necessary for existence, but the quantity of O absorbed must bear a direct relation to the degree of activity. The avidity of the different tissues for O varies greatly, and the differences are doubtless expressions, broadly speaking, of the relative intensities of their respiratory processes. Quinquaud[1] records the following absorption-capacities of 100 grams of each tissue, submitted for three hours to a temperature of 38° :

Muscle	23 c.c.	Spleen	8	c.c.
Heart	21 "	Lungs	7.2	"
Brain	12 "	Adipose tissue	6	"
Liver	10 "	Bone	5	"
Kidney	10 "	Blood	0.8	"

The quantity of CO_2 formed in each case was approximately proportional to the quantity of O absorbed. The respiratory value of blood is doubtless too low. The blood is not merely a carrier of O and CO_2 to and from the tissues, but is itself the seat of active disintegrations which involve the consumption of O and the production of CO_2 and other effete matters. Ludwig and his pupils long ago showed that when readily-oxidizable substances, such as lactate of sodium, are mixed with the blood, and the blood is transfused through the lungs or other living tissues, more O is consumed and CO_2 given off than by

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[1] *Comptes rendus de la Société de biologie* (9), 1890, 2, pp. 29, 30.

blood free from them. These results have been substantiated by the recent researches of Bohr and Henriquez[1] on dogs; these experiments have further shown that a considerable portion of O may disappear as a result of processes occurring in the blood during its passage through the lungs, and a large amount of CO_2 be formed as one of the products. Thus they found that considerably more O was absorbed from the lungs than could be pumped from the blood, and that more CO_2 was given to the air in the lungs than was lost by the venous blood. They believe that the tissues deliver to the blood partially-oxidized substances which undergo a final splitting up when the blood reaches the lungs. If this be so, the respiratory capacity of the blood, apart from its capacity as a carrier of O and CO_2 to and from the tissues, must be considerably greater than indicated by Quinquaud's figures.

The chief chemical product of the oxidative decompositions in the blood and tissues is CO_2; but the quantity of O absorbed is not necessarily related to the amount of CO_2 eliminated; that is, during a given interval the quantity of O may be out of proportion to the elimination of CO_2, and *vice versâ.* Thus, in a muscle during rest, at normal bodily temperature, the consumption of O is greater than the elimination of CO_2, while during activity the proportion of CO_2 to O increases and may exceed that of O. Rubner's[2] experiments on the resting muscle at various temperatures accentuate the fact that the formation of CO_2 may be independent of the quantity of O absorbed. Thus, at 8.4° the respiratory quotient was 3.28; at 28.2°, 1.01; at 33.8°, 1.18; and at 38.8°, 0.91. The high respiratory quotient at low temperatures is to be explained partly by direct oxidation and partly by intramolecular splitting, which is independent of oxidation. It is probable that during rest O is utilized to some extent in oxidations which are not at once carried to their final stage and in which relatively little CO_2 is formed; hence during activity comparatively little O is required to cause a final disintegration of the now partially broken-down substances, and thus to give rise to a relatively large formation of CO_2. (See Effects of Muscular Activity on Respiration and Metabolism of Muscle, etc.)

C. The Rhythm, Frequency, and Depth of the Respiratory Movements.

The Rhythm of the Respiratory Movements.—During normal breathing the respiratory movements follow each other in regular sequence or rhythm. Various instruments have been devised for the study of these movements in man; the form most commonly used is the stethograph or pneumograph of Marey. The respiratory movements are communicated by a system of levers to a tambour, thence through a rubber tube to a second tambour having attached a lever which records upon a moving surface. In animals a tracheal cannula or tube (p. 554) is usually inserted into the trachea, and a tube is led from it to a recording tambour. In case the movements

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[1] *Comptes rendus,* 1892, vol. 114, pp. 1496–99.
[2] *DuBois-Reymond's Archiv für Physiologie,* 1885, pp. 38–66.

of the ribs are especially to be studied, the stethograph may be employed; if the movements of the diaphragm, a long probe may be inserted through the abdominal walls so that one end rests between the liver and the diaphragm and the other end connects with a recording lever, the abdominal walls serving as a fulcrum. A tracing obtained by one of the above methods shows: (1) That inspiration passes into expiration without an appreciable intervening pause; (2) that inspiration is shorter than expiration; (3) that the curves of inspiration and expiration differ in certain characters. The relative periods of inspiration and expiration vary with age, sex, and other conditions. The inspiratory phase is shorter relatively in women than in men, and in children and the aged than in those of middle life. The length of inspiration as compared to expiration is subject to variations, but these relations are affected chiefly by disease and by other abnormal conditions. After section of the pneumogastric nerves, and in diseased conditions which narrow any part of the air-passages, inspiration is longer than expiration, while in emphysema the expiratory phase is prolonged. The relative periods occupied by inspiration and by expiration in the adult differ according to various observers; at one extreme, the ratio according to Vierordt and Ludwig is 10 : 19–20, and at the other extreme, according to Ewald, 11 : 12. A mean ratio is 5 : 6. Rennebaum found that the expiratory phase is relatively prolonged by an increase in the respiration-rate, the ratio being 9 : 10 at 13 respirations per minute, and 9 : 13 at 46 per minute. In the new-born the ratio is 1 : 2–3. Mosso found that during sleep the inspiratory phase is lengthened one-fourth.

Inspiration is more abrupt than expiration, the lever moving more rapidly during inspiration than during expiration; consequently the curves differ in character. We may volitionally affect the rhythm and the various phases of each respiratory act.

A pause may exist between expiration and inspiration (expiratory pause) when the respirations are abnormally infrequent. In certain diseases an interval may be observed between inspiration and expiration (inspiratory pause). Some observers look upon the nearly horizontal part of the respiratory curve as a record of a pause, but an examination of tracings of normal respirations shows that one phase passes into the other without an appreciable interval.

The respiratory acts while we are awake and quiet are rhythmical, but this rhythm is more or less disturbed during sleep, especially in young children and in the aged. In the latter there may not only be an irregularity in the time-intervals between successive acts, but occasionally long expiratory pauses, giving the movements a peculiar periodical character. In the so-called "Cheyne-Stokes respiration" the rhythm is greatly disturbed. This type is characterized by groups of respiratory movements, each group being separated from the preceding and succeeding ones by more or less marked pauses. The first respiration in each group is very shallow and is followed by movements which successively become deeper and deeper until a maximum is reached; then the successive movements become more and more shallow and finally cease. Each group commonly consists of about 10 to 30 respirations, and is

separated from the preceding and succeeding groups by a variable interval, usually 30 to 45 seconds. This form of respiration is frequently observed in uræmia, after severe hemorrhage, and in certain diseases of the heart and brain. Periodical alterations in the respiratory rhythm may be observed in the last stages of asphyxia, in poisoning by chloral, opium, curare, and digitalis, in certain septic fevers, in certain animals during hybernation, etc. In the human organism, excepting during sleep and in the aged and the very young, such non-rhythmical respirations are always indicative of abnormal conditions.

In warm-blooded animals the movements are generally of a much more rhythmical character than in cold-blooded animals.

The Frequency and Depth of the Respiratory Movements.—The respiratory rate is affected by a number of conditions, chiefly species, age, posture, time of day, digestion, activity, internal and external temperature, season, barometric pressure, emotions, the composition of the air, the composition of the blood, the state of the respiratory centres and nerves, etc.

The following figures, compiled from various sources, indicate the wide differences in various *species*, the rates being per minute:

Horse	6–10	Pig	15–20	Rabbit	50– 60
Ox	10–15	Man	16–24	Sparrow	90
Sheep	12–20	Cat	20–30	Guinea-pig	100–150
Dog	15–25	Pigeon	30	Rat	100–200

The average rate in man varies according to different investigators, from 11.9 by Vierordt to 19.35 by Ruef. Hutchinson noted 16–24 per minute as a mean of 2000 observations. There is a general, but not an absolute, relationship between the rate and the *size of the body*, as regards both different species and different individuals of the same species: as a rule, the smaller the species the more frequent the respirations; the same holding good for individuals of the same species.

The marked influence of *age* is illustrated by the records of the observations by Quetelet on 300 individuals:

Age.	Rate per Minute.		
	Maximum.	Minimum.	Mean.
New-born	70	23	44
1– 5 years	32	..	26
15–20 "	24	16	20
20–25 "	24	14	18.7
25–30 "	21	15	16
30–50 "	23	11	18.1

Posture exerts a marked influence, especially in those enfeebled by disease. Guy records, in normal individuals, 13 while lying, 19 while sitting, and 22 while standing.

The *diurnal changes* are in close accord with those of the pulse-rate (p. 412). The rate is less frequent by about one-fourth during the night than during the day, and more frequent after meals, especially after the mid-day meal. Vierordt noted the following variations: 9 A. M., 12.1; 12 M., 11.5; 2 P. M., 13;

7 p. m., 11.1. Guy gives the mean rate in the morning as 17 and in the evening as 18.

The rate increases with an increase in *muscular activity* (p. 413).

Changes in *external* (surrounding) *temperature* have very little influence. Vierordt noted a rate of 12.16 at 8.47° C. and one of 11.57 at 19.4° C., and that an increase of each degree C. decreases the period of each respiration 0.054. Alterations of *internal temperature* are associated with marked changes, as is well illustrated in the increase in the rate observed in fevers, which increase, in turn, is closely related to the rise in the pulse-rate and the bodily temperature.

Season is not without its influence. In the spring the rate, according to E. Smith, is 32 per cent. greater than at the end of summer.

Ordinary changes in *atmospheric pressure* exert no influence, but under considerable variations the rate rises and falls inversely with the pressure.

The frequency of the respirations may be profoundly affected by our *emotions* and by our *will*. Mental excitement may increase or decrease the rate, and, as is well known, we may greatly modify not only the rate but the depth of the movements by volitional effort.

If the *composition of the inspired air* becomes so altered that O falls below 13 volumes per cent., the respirations are increased in frequency and in depth. In the same way, if the blood becomes deficient in O or overcharged with CO_2, movements of respiration are increased.

Excitation and depression of the *respiratory centres* and *nerves* through the agency of operations, disease, poisons, etc. effect changes in the respiratory rate.

The rate and the depth of the respirations bear generally an inverse relation to each other : the greater the rate the less the depth, and *vice versâ ;* but the quantity of air respired during a given period does not necessarily bear any direct relation to either the rate or the depth alone, but rather to both.

A general relationship exists between the frequency of the respirations and the pulse-rate. Comparisons of a large number of observations by different investigators give a ratio at twenty-five to thirty-five years, 1 : 4–4.5 ; at fifteen to twenty years, 1 : 3.5 ; at six weeks, 1 : 2.5.

D. The Volumes of Air, O, and CO_2 Respired.

During quiet respiration there occurs an inflow and outflow of air, designated *tidal air,* equal to about 500 cubic centimeters, or 30 cubic inches. The volume of expired air is a little in excess of inspired air, owing to the expansion caused by the increase of temperature, although the actual volume is less (p. 519). The volume of air respired during each respiration bears generally an inverse relation to the respiration-rate, and is affected by the position of the body ; thus, if in the lying posture the volume be 1, when sitting it will be 1.11, and when standing 1.13 (Hutchinson). Besides the term *tidal air,* others are used to express definite volumes associated with the capacity of the lungs under certain circumstances. Thus, Hutchinson distinguishes

complemental air, or the volume that can be inspired after the completion of an ordinary inspiration (1500 cubic centimeters); *reserve* or *supplemental air*, or the volume that can be expelled after an ordinary expiration (1240–1800 cubic centimeters); *residual air*, or the volume remaining in the lungs after the most forcible expiration (1230–1640 cubic centimeters); and *stationary air*, or the volume remaining in the lungs after ordinary expiration, and equal to reserve air plus residual air (2470–3440 cubic centimeters). The volume of residual air is different according to various observers, the estimates ranging from 538 cubic centimeters by Kochs to 19,800 cubic centimeters by Neupauer. The recent researches of Hermann and Jacobson [1] give 914.5 cubic centimeters as the average of nine observations, the lowest measurement being 434 cubic centimeters, and the highest 1023.2 cubic centimeters.

Lung-capacity is the total quantity of air the lungs contain after the most forcible inspiration, and is equal to the vital capacity plus the residual air.

Bronchial capacity is the capacity of the trachea and bronchi, and is equal to about 140 cubic centimeters.

Alveolar capacity is the volume of air in the smallest air-passages and alveoli, and is greater during inspiration than during expiration, and, of course, is altered in proportion to the depth of these movements. After quiet expiration it is equal to about 2000 to 3000 cubic centimeters; during quiet inspiration it is increased about 500 cubic centimeters, and during forced inspiration about 2000 cubic centimeters; during forced expiration it is diminished about 1500 cubic centimeters. Between the extremes of forced inspiration and forced expiration the volume differs about $3\frac{1}{2}$ times.

Vital capacity is the volume of air that can be expired after the most forcible inspiration. Averages obtained by Vierordt from the results of the observations by various investigators are 3400 cubic centimeters for men and 2500 cubic centimeters for women. Such investigations are conducted by the aid of a spirometer (Fig. 138), which is a calibrated gasometer consisting of a bell-jar submerged in water and counterpoised. Communicating with the interior of the jar is a tube through which the expired air

Fig. 138.—Wintrich's modification of Hutchinson's spirometer.

is conducted. The subject makes the deepest possible inspiration and then forcibly expires into the tube: the jar rises in proportion to the volume of air admitted, and the extent of this rise may be read from the scale.

[1] *Pflüger's Archiv für Physiologie*, 1888, vol. 43, pp. 236, 440.

Vital capacity is affected by various circumstances, especially age, stature, sex, posture, occupation, and disease. It increases with age, reaching a maximum at about thirty-five years, after which there occurs an annual decrease of about 32 cubic centimeters up to about sixty-five years. In proportion to the length of the body it increases up to twenty-five years and then diminishes. Wintrich has shown that vital capacity for each centimeter of height varies at different ages; thus at eight to ten years it is 9 to 11 cubic centimeters for each centimeter of height, at sixteen to eighteen years 20.65 cubic centimeters, and at fifty years 21 cubic centimeters. Arnold estimates that in the adult for each centimeter of increase or decrease of height beyond a mean standard there is a corresponding rise or fall of 60 cubic centimeters in men and of 40 cubic centimeters in women. It is greater in men than in women of the same height, the ratio being about $10 : 7.5$. Hutchinson found that it was affected by posture, the ratios being as follows: Lying on chest and abdomen, 0.96; lying on back or sitting, 1.11; and standing, 1.13. Wintrich and Arnold both have found that vital capacity is diminished during starvation 100 to 200 cubic centimeters. Physical exercise, such as running and other forms of violent exertion that increase the rate and depth of respiration, tends to increase the vital capacity. Occupation also exerts an influence upon vital capacity, it being proportionately greater in those engaged in active physical work than in those leading a sedentary life. All circumstances which interfere with the full and free expansion of the thoracic cavity diminish vital capacity, as, for instance, tight clothing, visceral tumors, tuberculosis of the lungs, pneumothorax, etc.

The Volumes of O and CO_2 Respired.—The quantity of air respired during each respiratory act is about 500 cubic centimeters, or 30 cubic inches; and since the normal respiration-rate in man is, we may say, for the twenty-four hours about 15, the total quantity of air respired per diem may readily be calculated:

Per minute, 500 c.c. × 15 = 7,500 c.c., or 7.5 liters.
Per hour, 7.5 liters × 60 = 450 liters.
Per day, 450 liters × 24 = 10,800 liters, or about 380 cubic feet, which is equal to a volume about 220 centimeters ($7\frac{1}{3}$ feet) in height, width, and thickness.

With these figures as standards, and knowing the per cent. composition of inspired and expired air, the volumes of O absorbed and of CO_2 eliminated are easily found. The inspired air loses 4.78 volumes per cent. of O; it is obvious, then, that the quantity absorbed per diem is 4.78 volumes per cent. of 10,800 liters, which is 516 liters, or about 740 grams; likewise, the expired air contains an excess of 4.34 volumes per cent. of CO_2; the quantity expired per diem is 4.34 volumes per cent. of 10,800 liters, or 470 liters or 925 grams. These figures, while not strictly accurate, are in accord with those obtained by other methods of estimation and by experiments. The amount of O varies from 600 to 1200 grams per diem, and that of CO_2 from 700 to 1400 grams—approximate averages being about 750 grams of O and 875 grams of CO_2.

The quantities of O and of CO_2 exchanged, although in a general way closely related, are in a measure independent of each other, but, as a rule, an increase or a decrease in one is accompanied by a rise or a fall in the other. The most important conditions affecting the quantities of O absorbed and CO_2 given off are species, body-weight and body-surface, age, sex, constitution, rate and depth of the respirations, the period of the day, digestion, food, internal and external temperature, activity, atmospheric pressure, the composition of the inspired air, and the condition of the nervous system.

Most of the studies have been made solely by determinations of the quantities of CO_2 given off, the results being taken as standards for the relative volumes of O absorbed; but such deductions are of very uncertain value and may be entirely misleading. (See Respiratory Quotient, p. 544.)

Respiratory activity in different *species* in proportion to body-weight is less in cold-blooded than in warm-blooded animals, the difference being due chiefly to the larger supply of O demanded by the more active heat-producing processes in the latter, and in part to the more active character generally of the bodily operations. If we take as a standard for cold-blooded animals the respiratory activity in the frog (which is 0.07 gram of O per kilogram of body-weight per hour), and compare this with the standards for warm-blooded animals, in the latter it will be from 6 to 18 times greater, according to the species. Respiratory activity is higher in proportion to body-weight in birds than in mammals. The following tabular statement of the intensity of the respiratory interchange per kilogram of body-weight per hour, compiled chiefly from the researches of Regnault and Reiset, Zuntz and Lehmann, Bossignault, Herzog, and Grouven, illustrates these differences:

Animal.	O.		CO_2.		$\dfrac{CO_2}{O}$.
	Grams.	C.c.	Grams.	C.c.	
Finch	11.635	1837	11.540	5857	0.72
Sparrow	9.595	6710	10.492	5334	0.79
Fowl	1.189	831	1.271	678	0.82
Frog	0.070	49	0.062	37	0.76
Dog	1.191	847	1.281	652	0.77
Cat	1.001	699	1.082	549	0.80
Ox	0.550	382	0.757	383	1.00
Ass	0.566	394	0.393	394	1.00
Calf	0.481	336	0.571	290	0.86
Horse	0.437	303	0.640	323	0.91
Sheep	0.499	347	0.599	304	0.88
Rabbit	0.920	642	1.158	588	0.90
Man	0.434	302	0.507	257	0.85
Pig	0.474	331	0.594	302	0.91

As a rule, the smaller the species the greater (relatively, but not absolutely) is the intensity of respiratory activity; for instance, the consumption of O for each kilogram of body-weight is for the horse, 0.437; ass, 0.566; sheep, 0.499; rabbit, 0.92; and for birds, as high as 12.58. For different species of the same class the same variations are observed; thus, Richet records, as the result of investigations on birds, the following figures as the number of

grams of CO_2 given off per kilogram of body-weight per hour: Goose, 1.49; fowl, 1.66; duck, 2.27; pigeon, 3.36; and finch, 12.58.

In the same species, other things being equal, the respiratory interchange is greater in smaller animals, because in relation to *body-weight* the *body-surface* is greater, causing a greater proportional heat-loss, which in turn necessitates a larger consumption of O for oxidative processes to produce heat, and a consequent increase in the production of CO_2. Richet[1] has shown that in the same species the quantity of CO_2 exhaled (indicating the intensity of the oxidation-processes) is inversely proportional to the body-weight and is directly proportional to the body-surface. The following figures illustrate these important facts:

Mean Body-weight (kilograms).	CO_2 per Kilogram per Hour (grams).	Body-surface (sq. cm.).	CO_2 per 100 sq. cm. (grams).
24	1.026	9296	2.65
11.5	1.380	5656	2.81
6.5	1.624	3940	2.69
3.1	1.964	2341	2.71

Thus, an animal weighing 24 kilograms will give off 1.026 grams of CO_2 per hour for each kilogram of body-weight, while one weighing 3.1 kilograms will give off 1.964 grams, or nearly twice as much, for equal increments of weight. It will be observed by comparing the quantity of CO_2 and the body-surface that for each 100 square centimeters of surface the elimination is about the same.

Age exercises an important influence. Until full growth respiratory activity is higher than in middle life, and in middle life it is higher than in old age. In children the absolute quantities of O consumed and CO_2 formed are less than in the adult, but in relation to body-weight they are about twice as much. During middle life respiratory activity is about one-sixth higher than during old age. In the young the quantity of O in relation to CO_2 is higher than in the adult.

Andral and Gavarret have shown, in investigations relative to *sex*, that after the eighth year males give off from one-third to one-half more CO_2 than females, the difference being most pronounced at puberty. During pregnancy and after the menopause the relative quantity of CO_2 rises.

The influence of *constitution* is manifest by a greater intensity of respiratory activity in the robust than in the weak, other conditions being the same.

The *rate and depth of the respiratory movements* do not appreciably affect the volumes of O and CO_2 interchanged, although the removal of CO_2 is facilitated by an increase of the volume of air respired, because of the better ventilation of the lungs. An increase in the rate, the depth remaining constant, increases the volume of air respired and the absolute quantity of CO_2 given off, but the quantity of CO_2 in relation to the total volume of air is less. If

[1] *Archiv de Physiologie normale et pathologique*, vol. 22, pp. 17–30.

the rate remain constant and the depth be increased, similar results are obtained.

The quantity of CO_2 eliminated during slow, deep respirations is larger than during rapid, shallow respirations.

The *diurnal variations* are in accord with the changes in the respiratory rate—rising after we awake, falling during the forenoon, again rising after the mid-day meal, again falling during the afternoon, increasing after the evening meal, and falling to a minimum during the night.

Sunlight exercises a marked influence, as is proven by the results obtained by a number of investigators. In frogs the elimination of CO_2 is increased by sunlight, even after excision of the lungs. Fubini and Benedicenti,[1] in experiments upon hybernating animals, found that the comparative quantities of CO_2 eliminated under the influence of sunlight and of darkness were as 100 : 93.48. Confirmatory results have been obtained by Ewald on curarized frogs.

Respiratory activity is affected by the character and quantity of the *food*. The following results, obtained by Pettenkofer and Voit, are very instructive :

	Fasting.	Mixed Diet.	Non-nitrogenous Diet.	Nitrogenous Diet.
O	743 grams.	867 grams.	808 grams.	1083 grams.
CO_2	695 "	930 "	839 "	850 "

It will be observed that respiratory activity is lowest during fasting, higher when the diet is non-nitrogenous, still higher when the diet is mixed, and highest when the diet is purely nitrogenous. The respiratory quotient is higher when the diet is rich in carbohydrates (p. 545), while it falls in proportion to the percentage of nitrogenous food. Fasting reduces the quotient considerably, and if coupled with inactivity (hybernation) causes it to fall to a minimum.

During *digestion* the gaseous exchange is increased, according to Loewy,[2] from 7 to 30 per cent. Joylet, Bergonie, and Sigalas[3] obtained the following averages of seven experiments on a man weighing 52 kilograms, the increase of O being about 7 per cent., and of CO_2 about 6 per cent. :

	O.	CO_2.	$\frac{CO_2}{O}$.
Before food	259 grams.	298.4 grams.	0.869
After food	275 "	317 "	0.867

The increase of respiratory activity during digestion may be due to the chemical processes involved in the production of the digestive secretions, to the oxidation of the products of digestion after absorption, or to muscular activity of the gastro-intestinal walls. Zuntz and Mering[4] endeavored to

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[1] *Moleschott's Untersuch. z. Naturl.*, 1887, vol. 14, pp. 623–629.

[2] *Pflüger's Archiv f. Physiologie*, 1888, vol. 43, pp. 515–532.

[3] *Compt. rend.*, 1887, vol. 105, pp. 380, 675.

[4] *Pflüger's Archiv f. Physiologie*, 1883, vol. 32, pp. 173–221.

settle this point by making three series of experiments: in one they injected certain readily oxidizable substances into the blood; in another the substances were injected into the stomach; and in another sulphate of sodium or other purgative was given. When the substances were injected into the blood, Zuntz and Mering found as a general result that the absorption of O was not increased, while the formation of CO_2 was slightly increased; when injected into the stomach, no marked increase in respiratory activity occurred unless the substances were given in large quantities. When, however, in addition to the readily oxidizable substances, a purgative was injected, or when the purgative was given alone, the absorption of O and the elimination of CO_2 were considerably increased. They were therefore led to conclude that the increased respiratory interchange during digestion is due chiefly to the muscular activity of the intestinal walls. Loewy [1] has confirmed this conclusion, and has clearly shown that the increase in respiratory activity is chiefly related to the intensity of peristalsis, the most marked increase being associated with excessive peristaltic activity. There can be no reasonable doubt, however, that an insignificant portion of the increase is due both to glandular activity and to the oxidation of the absorbed products of digestion.

The volumes of O absorbed and of CO_2 produced rise with an increase of *bodily temperature.* This fact has been illustrated by the experiments of Pflüger and Colasanti on guinea-pigs, in which they found that the quantity of O absorbed at a bodily temperature of 37.1° was 948.17 grams; at 38.5°, 1137.3 grams; at 39.7°, 1242.6 grams. Similar results have been obtained by other investigators in experiments both upon the human subject and upon the lower animals under the pathological conditions of fever. A fall of bodily temperature is accompanied by a decrease in the intensity of respiration, unless the fall is accompanied by muscular excitement, such as shivering. Speck [2] has seen shivering cause the consumption of O to rise from 302 to 496 cubic centimeters, and the exhalation of CO_2 from 287 to 439 cubic centimeters. The primary and fundamental effect of lowering the bodily temperature is to diminish respiratory activity, but this may be more than compensated for by involuntary or voluntary excitement of the muscles (p. 541; see also Tissue-respiration).

The effects of *external temperature* upon warm- and cold-blooded animals are different: Moleschott found that frogs produced three times more CO_2 at 38.7° than at 6°, while in warm-blooded animals the opposite is the case—that is, three times more CO_2 is formed at the lower temperature. The frog's temperature rises and falls with changes in the temperature of the surroundings, while that of warm-blooded animals remains at a fairly constant standard; hence the respiratory intensity in the frog increases with the rise of external temperature, while in warm-blooded animals it decreases, owing to diminished heat-production. But in warm-blooded animals the alterations in respiratory activity caused by changes of external temperature are not always in inverse relation. Thus, Voit has shown, as a result of studies in man, that the exhala-

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[1] *Loc. cit.*   [2] *Deutsches Archiv f. klin. Med.,* 1889, vol. 33, pp. 375, 424.

tion of CO_2 diminishes with the rise of external temperature from 4.4° until the temperature reaches 14.3°, when it rises slowly. These results have been substantiated by the more recent investigations of Page,[1] who found in experiments on dogs that the discharge of CO_2 was at a minimum at about 25°; that below this temperature the quantity increased as the temperature fell; and that above this temperature the discharge increased, and became greatly augmented at temperatures of 40° to 42°. At the latter temperatures the increase may reach $3\frac{1}{2}$ times the normal, but the *bodily temperature* is also increased. If the elimination of CO_2 at 23° to 24° be represented by 100 as a standard, at 13° it will be about 128; at 10°, 141; and at 18°, 177. The researches of Speck,[2] of Loewy,[3] and of Quinquaud[4] all show that external cold increases respiratory activity, chiefly by causing involuntary muscular excitement (shivering). If shivering and other forms of muscular activity be absent, the exchange of O and CO_2 is unaffected or diminished, but when present the increase of respiratory activity may amount to 100 per cent. notwithstanding a fall of bodily temperature below the normal.

Muscular activity is one of the most important of all the circumstances affecting the quantities of O and CO_2 exchanged. Involuntary excitement, such as shivering, may of itself double the consumption of O and increase by one-half the elimination of CO_2, but the volitional effort may increase the interchange even beyond these limits. Hirn, in investigations on four men, noted during rest an hourly absorption of 30.2 grams of O, and during work 120.9 grams; and Pettenkofer and Voit, in similar studies, found an increase of O from 867 grams during rest to 1006 grams during moderate work, and from 930 grams of CO_2 to 1137 grams. In experiments on the horse Zuntz and Lehmann[5] obtained the following results, which show to what a marked extent the respiratory interchange may be increased by muscular activity:

	Liters per Minute.		
	O.	CO_2.	$\frac{CO_2}{O}$.
Resting	1.722	1.570	0.92
Walking	4.766	4.342	0.90
Trotting	8.093	7.516	0.93

Speck[6] has added some interesting facts to our knowledge of the effects of muscular activity on the respiratory interchange. Thus, he found that the increase of O and CO_2 reaches a maximum before exertion reaches its maximum; that the increase for the same amount of work can be varied by changing the position of the body; that if a given amount of work be divided into two equal parts, the increase of respiratory activity during the first period is greater than during the second; that the greater the increase of CO_2, the less,

[1] *Journal of Physiology*, 1879–80, vol. 2, p. 228.   [2] *Loc. cit.*

[3] *Pflüger's Archiv f. Physiologie*, 1890, vol. 46, pp. 189–224.

[4] *Compt. rend.*, 1887, vol. 104, pp. 1542–1544.

[5] *Journal of Physiology*, 1890, vol. 2, p. 396.

[6] *Deutsches Archiv f. klin. Med.*, 1889, vol. 45, pp. 460–528.

proportionately, is the increase of O, so that the respiratory quotient rises more and more, and to such an extent that the CO_2 contains more O than is at the time absorbed; and that the quantity of air respired is so intimately related to the amount of CO_2 given off that he regards the quantity of this gas formed as the regulator, as it were, of the degree of activity of the respiratory movements.

Grüber [1] states that while respiratory activity is proportional to the intensity of muscular activity, "training" diminishes the quantity of CO_2 given off for the same amount of work. Thus, taking 1 as a standard of the amount of CO_2 eliminated during rest, he obtained the following ratios in two series of observations:

	Resting.	Walking.	Climbing hills when not used to it.	Climbing hills when used to it.
First series	1	1.89	4.1	3.3
Second series	1	1.75	3.05	2.42
Mean	1	1.82	3.07	2.86

Training therefore reduces the output about 20 per cent.

The elimination of CO_2 is about one-fifth less during sleep than while awake and quiet; from one-fifth to one-half greater during ordinary exertion; from two to two and a half times greater during violent exercise; and about three times greater during tetanus.

During hybernation the absorption of O falls to $\frac{1}{41}$ and the elimination of CO_2 to $\frac{1}{75}$ of the normal for the period of activity (Valentine). Relatively more O is absorbed than CO_2 given off, hence the respiratory quotient falls, reaching as low as 0.50 to 0.75.

A diminution of the *barometric pressure* increases the respiration-rate and the volume of air respired, but both Mosso and Marcet have shown that if allowances be made for the increase of volume of the air at the lower pressure, the actual volume respired is less. Conversely, an increase of pressure lowers the rate and the volume of air respired. Extremes of pressure severely affect the respiratory and other functions (p. 559).

The integrity of the *nervous apparatus* which governs the metabolic processes in the tissues is obviously of fundamental importance. If the efferent nerve-fibres of a muscle be cut, the interchange of O and CO_2 at once sinks, as illustrated by the following results obtained by Zuntz:

	O consumed.	CO_2 given off.
Before section	13.2 c.c.	14.4 c.c.
After section	10.45 c.c.	10.1 c.c.
After section (less)	2.75 c.c.	4.3 c.c.

The consumption of O was therefore lessened about 20 per cent., and the formation of CO_2 about 30 per cent.

After section of the spinal cord in the dorsal region Quinquaud [2] obtained

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[1] *Zeitschrift f. Biologie*, 1891, vol. 28, pp. 466–491.

[2] *Compt. rend. Soc. Biologie*, 1887, pp. 340–342.

similar results. Before the section the blood in the crural vein contained 9.5 per cent. of O and 60 per cent. of CO_2; after section it contained 13.5 per cent. of O and 40 per cent. of CO_2, showing that the consumption of O by the tissues and the formation of CO_2 were considerably lessened. After destruction of the spinal cord respiratory activity falls to a minimum.

The study of the effects of *alterations in the composition of the inspired air* on the absorption of O and the elimination of CO_2 are of great importance. Nitrogen is merely a mechanical diluent of the inspired air, and may be replaced by H or by other inert gas, so that alterations in its percentage do not, *per se*, affect the respiratory phenomena; but changes in the percentages of O and CO_2 may cause marked disturbances both of the respiratory movements and of the gaseous interchange.

When the percentage of O in the inspired air is increased up to 40 volumes per cent., Bert found that there occurred an increase in the quantity absorbed, and both Speck and Fredericq have noted merely a transient increase under similar circumstances; but the results of most experimenters, on the contrary, seem to show quite conclusively that an increase of the per cent. of O above the normal does not affect the quantity absorbed. Lukjanow[1] in a large number of experiments could not detect any increase, and Saint-Martin,[2] in researches on guinea-pigs and rats with an atmosphere containing from 20 to 75 volumes per cent. of O, noted the same result. Even in an atmosphere of pure O animals breathe as though they were respiring normal atmospheric air.

A decrease in the percentage of O is without influence until the proportion falls below 13 volumes per cent. Worm-Müller long ago showed that animals breathe quietly in air containing 14.8 volumes per cent. of O, and that if the proportion fell to 7 volumes per cent., respiration became slow, deep, and difficult; with 4.5 volumes per cent. marked dyspnœa occurred; and when there was but 3 volumes per cent. asphyxia rapidly supervened. The more recent results of Speck[3] not only confirm the main facts of Worm-Müller's observations, but furnish other important data. He has shown that when the atmosphere contains 13 volumes per cent. of O, respiration is quiet and the quantity of O absorbed is but slightly, if at all, diminished, and that even when the proportion falls to 9.65 volumes per cent. breathing is carried on for a long time without inconvenience, the amount of O absorbed, however, being diminished. He shows, moreover, that when the volume of O in the atmosphere falls to 8 per cent. the respiratory movements are deep and are but slightly accelerated, the quantity of O absorbed being very much diminished, and that the animal subjected to such an atmosphere succumbs in a few moments. The quantity of O taken into the lungs falls proportionately with the diminution of O in the inspired air until the reduction reaches 11.26 volumes per cent., but further diminution is compensated for by an increase in the volume of air respired. As the volume per cent. of O in the inspired air

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[1] *Zeitschrift f. Physiolog. Chemie*, 1883–1884, vol. 8, pp. 313–355.

[2] *Compt. rend.*, 1885, vol. 98, pp. 241–243.

[3] *Zeitschrift f. klin. Med.*, 1887, vol. 12, pp. 447–532.

diminishes the relative percentage of O absorbed increases, and this continues until the volume in the inspired air is reduced .to 11.26 per cent., 27 per cent. of which is absorbed; below this point no further increase of absorption occurs. As the quantity of O absorbed is reduced the respiratory quotient becomes greater, and may reach as high as 2.218.

When the quantity of O remains at the normal standard and the percentage of CO_2 is much increased, the elimination of the latter is interfered with; and Pflüger has shown that if the percentage of CO_2 be high, dyspnœa ensues, notwithstanding the fact that the blood contains a normal amount of O. When air contains 3 to 4 volumes per cent. of CO_2, the quantity of CO_2 given off is diminished about one-half. Speck[1] and others have found that the elimination of CO_2 during a given period may be independent of both the percentage of O in the inspired air and the quantity absorbed. An atmosphere containing 10 volumes per cent. of CO_2 is generally believed to be toxic, but Wilson's[2] investigations show that air having even as much as 25 to 30 volumes per cent. may be inhaled with impunity. It is quite probable that in those cases in which small percentages of CO_2 in the inspired air have proven poisonous the gases were contaminated with CO (carbon monoxide). Respiration of an atmosphere of pure CO_2 is followed within two or three minutes by death.

Worm-Müller found that when animals breathe atmospheric air in a *large* closed chamber O disappears and CO_2 accumulates, and death finally occurs, not from a lack of O, but from the increase of CO_2, as is shown by the fact that at the time of death the quantity of O in the air is sufficient to sustain life. He has also shown that animals placed in an atmosphere of pure O die from an accumulation of CO_2 in the blood, rabbits succumbing after the retention of a volume of CO_2 equal to one-half the volume of the body, and at a time when the atmosphere contained as much as 50 volumes per cent. of O.

The dyspnœa occurring in an animal confined in an air-tight chamber of *small* size is due to the lack of O, nearly all of the gas being absorbed before the animal dies. If a cold-blooded animal, such as a frog, be similarly exposed, the attraction of hæmoglobin for O is so strong that almost every particle of gas will pass into the blood long before death occurs; and even after the total disappearance of O the elimination of CO_2 is said to continue at the normal rate.

Animals placed in a confined space become accustomed, as it were, to the vitiated air, and survive longer than a fresh animal suddenly thrust into the poisonous atmosphere.

The Respiratory Quotient.—The relation between the quantities of O absorbed and CO_2 given off during a given period is expressed as the respiratory quotient. The air during its sojourn in the lungs loses 4.78 volumes per cent. of O and acquires 4.34 volumes per cent. of CO_2, hence the respiratory quotient is $\dfrac{CO_2,}{O,} \dfrac{4.34}{4.78} = 0.901$. This quotient is subject to considerable

[1] *Loc. cit.*   [2] *American Journ. Pharmacy*, 1893, p. 561.

variations not only in different species, but in different individuals under varied circumstances. The chief reasons for the differences are:

First, the production of CO_2 is in a measure independent of the O absorbed, as is proven by the records of various investigators, showing that CO_2 results both from oxidation-processes and from intramolecular splitting (analogous to fermentation-processes) which may be entirely independent of each other; that the quantity of CO_2 eliminated may continue under certain circumstances at the normal standard even after the absorption of O has ceased; and that the quantity of O contained in the CO_2 eliminated during a given time may be larger than the actual quantity absorbed. This may be understood in a general way when we remember that the CO_2 formed in the body is not the result of an immediate oxidation of the carbon-containing material of the body; on the contrary, some of the O absorbed may be stored, as it were, in the form of complex compounds, which at some later time may undergo disintegration, with the formation of CO_2; or the complex materials introduced as food may undergo a similar disintegration and splitting of the molecules, with the formation of CO_2 independently of the direct action of the O upon them.

Second, a larger quantity of CO_2 is formed per unit of oxygen from the disintegration of certain substances than from others, consequently the quotient must be affected by the nature of the substances broken down. Thus, in the formation of CO_2 from carbohydrates all of the O consumed in the disintegration of the molecules is used in forming CO_2, the H already having sufficient O to satisfy it; but in the case of fats and proteids a portion of the O is utilized in the oxidation of H to form H_2O. 6 molecules of O will oxidize 1 molecule of grape-sugar $(C_6H_{12}O_6)$ into $6CO_2 + 6H_2O$; hence the quotient is $\dfrac{6CO_2}{6O_2} = 1$. In regard to fat, if we take olein, $C_3H_5(C_{18}H_{33}O_2)_3$, as an example, 80 molecules of O are required to reduce each molecule of the fat to 57 molecules of CO_2 and 52 molecules of H_2O; hence the quotient is $\dfrac{57CO_2}{80O_2} = 0.712$. In the disintegration of proteid only a part of the C is oxidized into CO_2, the remainder being eliminated as a constituent of various complex effete bodies; but it is estimated that the quotient for proteids (albumin) is from 0.75 to 0.81, depending upon the completeness of disintegration.

The respiratory quotient varies with species, food, age, the time of day, internal and external temperature, muscular activity, the composition of the inspired air, etc.

In regard to *species*, the quotient is higher in warm-blooded (0.70 to 1.00) than in cold-blooded animals (0.65 to 0.75); in herbivora (0.90 to 1.00) than in carnivora (0.75 to 0.80); and in omnivora (0.80 to 0.90) than in carnivora, but lower than in herbivora. These differences are due essentially to *diet*, herbivora feeding largely upon carbohydrates, omnivora using carbohydrates to a less extent, and carnivora practically not at all. These observations are substantiated by the fact that during fasting, when the animal is feeding upon its own tissues, the respiratory quotient in all species is the same (0.7 to 0.75).

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The quotient is lowered by an animal diet and increased by a vegetable diet, the ratio approximating unity if the diet be sufficiently rich in carbohydrates. Hanriot and Richet [1] in observations on man noted that before feeding the quotient was 0.84 to 0.89; when meat or fat was given the consumption of O was increased, but there was no increase in CO_2, and the quotient fell to 0.76; when given potatoes it was 0.93; and when the diet was of glucose it reached 1.03. During fasting the quotient falls rapidly. The experiments of Zuntz and Lehmann [2] show that in dogs it falls as low as 0.65 to 0.68 on the second day of fasting, and that on the resumption of food it rises to 0.73 to 0.81.

The influence of *age* is manifest in the fact that in children the quotient is lower than in the adult, more O being absorbed in proportion to the CO_2 given off than after full growth has been reached.

The quotient undergoes a *diurnal variation*. The day-time is more favorable than the night for the discharge of CO_2, as well as for the absorption of O, owing mainly to greater muscular activity during the day, but the CO_2 is more affected than the O; hence the respiratory quotient is higher during the day. In the recent experiments by Saint-Martin [3] on birds, the mean quotient during the day was 0.83 and during the night 0.72; the ratio for CO_2 for the day and night was 1 : 0.78, and for O 1 : 0.9. During the night the elimination of CO_2 was diminished about 20 per cent., while the absorption of O fell only about 10 per cent.

The quotient is increased by a rise of *external temperature*. Thus, Pflüger and Finkler found in guinea-pigs that the quotient was 0.83 at 3.64° and 0.94 at 26.21°. When the *bodily temperature* is increased, as in fever, the respiratory quotient remains practically unaltered. When the temperature falls below the normal the respiratory quotient increases.

Muscular activity is also an important factor. During rest the consumption of O by muscles is greater than the production of CO_2, while during contraction the difference becomes less and less in proportion to the degree of activity, until finally more CO_2 may be given off than there is O consumed. Sczelkow found in experiments on muscles of rabbits at rest and in tetanus that the respiratory quotient was decidedly increased. A mean of six experiments gives as the quotient during rest 0.543 and during tetanus 0.933; in one-half of the experiments it went above 1, and in one instance to 1.13.

During sleep the output of CO_2 is diminished more than the consumption of O (p. 542), so that the respiratory quotient is less than when awake and quiet.

During hybernation the quotient falls to a minimum—in the marmot as low as 0.49. This is due chiefly to the more decided falling off in the quantity of CO_2, the CO_2 being reduced to $\frac{1}{75}$, and the O to only $\frac{1}{41}$; the animal, however, is not only in a state of muscular quiet, but fasting, which, it will be remembered, is an important factor in lowering the quotient.

[1] *Compt. rend.*, 1888, vol. 106, pp. 496–498.

[2] *Berliner klin. Woch.*, 1887, p. 428.

[3] *Compt. rend.*, 1887, vol. 105, pp. 1124–1128.

When the *percentage of O in the inspired air* falls so low as to cause marked dyspnœa, the respiratory quotient rapidly rises. This is owing on the one hand to the diminished quantity of O absorbed, and on the other hand to the increased production of CO_2 as a consequence of excessive activity of the muscles of respiration. Speck (p. 543) found that when the proportion of O was very low the quotient rose as high as 2.258.

E. PRINCIPLES OF VENTILATION.

Breathing within a confined space, as in a small unventilated room or in a large room in which a considerable number of persons are assembled, causes a gradual diminution in the quantity of O and an accumulation of CO_2, moisture, and organic matter. In regard to O, even in the worst ventilated rooms the atmosphere seldom contains as little as 15 volumes per cent., which is sufficient to permit of undisturbed respiration. When the proportion of CO_2 exceeds 0.07 volume per cent. the air becomes disagreeable, close, and stuffy—offensive characters which are due neither to the increase of CO_2 nor to a deficiency of O, but to the presence of organic matter termed "crowd-poison." Air from which this organic exhalation is absent may contain considerably more CO_2 without causing any unpleasant effects. In well-ventilated rooms the proportion of CO_2 does not exceed 0.05 to 0.07 volume per cent.; in badly-ventilated rooms it may reach 0.25 to 0.30 volume per cent.; while when a large number of individuals are crowded together, as in lecture-rooms, it may be as high as 0.70 to 0.80 volume per cent. This vitiation is further increased by the burning of gas or oil, 150 liters of ordinary coal-gas (enough to supply a large burner for about an hour) consuming all the O in 1200 liters of air, or as much O as is required by the average individual in eight hours, besides loading the air with various deleterious products of combustion.

While the accumulation of CO_2 even in the worst ventilated rooms is not in itself pernicious, its percentage is a practical working index of the amount of organic matter present, and therefore of the degree of vitiation. It has long been recognized that the atmosphere of crowded, badly-ventilated rooms is poisonous, but the precise nature of the toxic element is unknown. Brown-Séquard and d'Arsonval condensed the moisture of the expired air and found that from 20 to 40 cubic centimeters would kill a guinea-pig; but their results have been contradicted positively by Dastré and Loye, Lehmann, Geyer, and others. The poison in expired air, whatever it may be, is of an impalpable nature, and is neither dissolved nor condensed in the moisture exhaled.

The quantity of fresh air required during a given period depends upon the size of the individual, the degree of activity, and the size of the air-space. Assuming that an individual eliminates 900 grams, or 458 liters, of CO_2 per diem, and that the percentage of CO_2 is to be kept at a standard not exceeding 0.07 volume per cent., there would be required at least 1,440,000 liters of fresh air during twenty-four hours, or about 60,000 liters (2000 cubic feet) per

hour. All circumstances, such as muscular activity, which increase the output of CO_2 augment the demand for fresh air. When confined in rooms, every person should have an air-space equal to about 28,000 liters, or 1000 cubic feet, the floor-space should not be less than $\frac{1}{10}$ of the cubic capacity of the room, and the air should be renewed as often as twice an hour. In lecture-rooms, school-rooms, etc. the air-space per individual is usually very small, so that the renewal must be more frequent and in proportion to the limitation of space per individual.

Ventilation is accomplished by natural and artificial means. The forces of the wind, the differences in temperature within and without the building, the natural diffusion of gases owing to variations in composition, etc., all cause more or less circulation. Artificial ventilation is effected by the use of proper appliances for the forced introduction of air into and expulsion from apartments.

F. The Effects of the Respiration of Various Gases.

The respiration of pure O takes place without disturbance of the respiratory processes, but dyspnœa is developed when the inspired air contains less than 13 volumes per cent. (p. 543). Respiration of pure CO_2 (p. 544) is fatal within two or three minutes, but an atmosphere containing as much as 25 to 30 per cent. may be respired for a few minutes without ill effect (p. 544). Nitrogen, hydrogen, and carburetted hydrogen (CH_4) may be inhaled with impunity if they contain not less than 13 volumes per cent. of O. The respiration of nitrous oxide or of air containing much ozone rapidly produces anæsthesia, unconsciousness, and death. Carbon monoxide (CO) and cyanogen are decidedly toxic, combining with hæmoglobin and displacing oxygen. Sulphuretted hydrogen, phosphoretted hydrogen, arseniuretted hydrogen, and antimoniuretted hydrogen are all poisonous and are all destructive to hæmoglobin. An atmosphere containing 0.4 volume per cent. of sulphuretted hydrogen is said to be toxic. Air containing 2 volumes per cent. of CO (carbon monoxide) is quickly fatal. Certain gases and vapors—as, for instance, ammonia, chlorine, bromine, ozone, etc.—produce serious irritation of the respiratory passages, and may in this way cause death.

G. Effects of the Gaseous Composition of the Blood on the Respiratory Movements.

Certain terms are employed to express peculiarities in the respiratory phenomena : *Eupnœa* is normal, quiet, and easy breathing. *Apnœa* is a suspension of the respiratory movements. *Hyperpnœa* is a condition of increased respiratory activity. *Polypnœa, thermopolypnœa,* and *heat-dyspnœa* are forms of hyperpnœa due to heating the blood or the skin. *Dyspnœa* is distinguished by deep and labored breathing ; the respiratory rate is usually less than the normal, but in some forms it may be higher. *Asphyxia* (suffocation) is characterized by infrequent, feeble, and shallow respirations.

Eupnœa is the condition of respiration observed during bodily and mental

quiet, the quantities of O and CO_2 in the blood being within the normal mean limits.

Apnœa may be produced by rapidly repeated respirations of atmospheric air, under which circumstances the respiratory movements may be arrested for a period varying from a few seconds to a minute or more. This condition is produced most easily upon animals which have been tracheotomized and connected with an artificial respiration apparatus. If under these conditions the lungs are repeatedly inflated with sufficient frequency, and the blasts are then suspended, the animal will lie quietly for a certain period in a condition of apnœa. The respirations after a time begin, usually with very feeble movements which quickly increase in strength and depth to the normal type. The ultimate cause of apnœa is still a mooted question, and the heretofore prevalent belief that it is due to hyperoxygenation of the blood is almost entirely discarded. The connection between the quantity of O in the blood and apnœa is, however, suggested by several facts: thus, apnœa is more marked after the respiration of pure O than after that of atmospheric air, and less marked if the air is deficient in O; moreover, Ewald states that the arterial blood of apnœic animals is saturated with O. These facts naturally lead to the inference that the blood is surcharged with O, and that the respiratory movements are arrested until the excess of O is consumed or until sufficient CO_2 accumulates in the blood to excite respiratory movements. But Head[1] has shown that apnœa can be caused by the inflation of the lungs with pure hydrogen as well as by inflation with air or with pure O, although the apnœic pause after the cessation of the inflations is not so long or may be absent altogether; while Ewald's assertion as to the saturation of the blood with O is contradicted by Hoppe-Seyler, Gad, and others. The fact that the apnœic pause exists for a longer period when O is respired lends confirmation to Gad's theory that it is due in part to the large amount of O carried into and stored up, as it were, in the alveoli— an amount sufficient to supply the blood for a certain period and thus to dispense with respiratory movements. Gad found that even when apnœa follows the inflation of the lungs with air, the air in the lungs contains enough O to supply the blood during the period occupied by the blood in making a complete circuit of the system. The fact, however, that apnœa can be caused by the inflation of the lungs by an indifferent gas such as hydrogen, by which every particle of O may be driven from the lungs, certainly shows that there exists some important factor apart from the O; and this assumption receives support in the observation that after section of the pneumogastric nerves (the channels for the conveyance of sensory impulses from the lungs to the respiratory centre) it is very difficult to cause apnœa by inflation of the lungs with air, while if pure hydrogen is used violent dyspnœa results. It seems, then, that apnœa cannot be produced after division of the vagi unless there be an accumulation of O in the lungs. These facts suggest that the frequent forced inflations of the lungs excite the pulmonic peripheries of the pneumogastric nerves, thus generating impulses which inhibit the inspi-

[1] *Journ. Physiology*, 1889, vol. 10, pp. 1, 279.

ratory discharges from the respiratory centre. This view receives further support in several facts: first, that the same number of inflations, whether of pure O, of air, or of H, causes apnœa, the only difference being the length of the apnœic pause after the cessation of artificial respiration, which pause lasts for the longest period when O is used, and for the shortest period, or not at all, when H is employed; second, that apnœa cannot be caused by inflation of the lungs with H if the pneumogastric nerves be previously divided; third, that the arrest of respiration which occurs during swallowing ("deglutition-apnœa") is due to an inhibition of the respiratory centre by impulses generated in the terminations of the glosso-pharyngeal nerves (p. 570). It therefore seems evident that apnœa may be due to either gaseous or mechanical factors, or to both, the former being effective, not because of the blood being saturated with O, but because of the increased amount of O in the alveoli—a quantity sufficient for a time to aërate the blood; while the mechanical factors give rise to inhibitory impulses which suspend for a longer or shorter period the rhythmical inspiratory discharges from the respiratory centre, doubtless by depressing the irritability of this centre (p. 563). From the experiment quoted it seems that the first of these factors may alone be sufficient to cause apnœa, but that apnœa is more easily produced, and lasts longer, when both factors act together, as is usually the case.

Polypnœa, thermopolypnœa, and *heat-dyspnœa* are due to a direct excitation of the respiratory centres through an increase of the temperature of the blood, or reflexly by excitation of the cutaneous nerves by external heat. This condition may be produced, as was done by Goldstein, by exposing the carotids and placing them in warm tubes, thus heating the blood; or, as was done by Richet and others, by subjecting the body to high external heat. Richet in employing this latter method found that dogs so exposed may have a respiratory rate as high as 400 per minute. Ott records marked polypnœa as a result of direct irritation of the tuber cinereum. This form of hyperpnœa is entirely independent of the gaseous composition of the blood; moreover, an animal in heat-dyspnœa cannot be rendered apnœic, even though the blood be so thoroughly oxygenated that the venous blood is of a bright arterial hue.

Dyspnœa is generally characterized by slow, deep, and labored respiratory movements, although in some instances the rate may be increased. Several distinct forms are observed: "O-dyspnœa," due to a deficiency of O; "CO_2-dyspnœa," due to an excess of CO_2 in the blood; a form of dyspnœa due to substances imparted to the blood by the muscles during activity; and *cardiac* and *hemorrhagic* dyspnœas, belonging to the O category.

Dyspnœas due to the gaseous composition of the blood may be caused either by a deficiency of O or by an excess of CO_2, but are generally due to both. Dyspnœa from a deficit of O is observed when an animal is placed within a *small* closed chamber, or when an indifferent gas, such as pure hydrogen or nitrogen, is respired. Under the latter circumstances dyspnœa occurs even though the quantity of CO_2 in the blood be below the normal. If, on the contrary, the animal be compelled to breathe an atmosphere containing 10 vol-

umes per cent. of CO_2, dyspnœa occurs, notwithstanding an abundance of O (p. 544) both in the air and in the blood; indeed, the quantity of O in the blood may be above the normal. Fredericq[1] in ingenious experiments has directly demonstrated the influence of the quantity of CO_2 in the blood upon the respiratory movements. He took two rabbits or dogs, A and B, ligated the vertebral arteries in each, exposed the carotids, and ligated one in each animal. The other carotid in each was cut, and the peripheral end of the vessel of one was connected by means of a cannula with the central end of the vessel of the other, so that the blood of animal A supplied the head (respiratory centre) of animal B, and *vice versâ*. When the trachea of animal A was ligated or compressed the animal B showed signs of dyspnœa, because its respiratory centre was now supplied with the venous blood from A. On the contrary, animal A exhibited quiet respirations, almost apnœic, because its centre received the thoroughly arterialized blood from B, in which the respiratory movements were augmented. In a second series of experiments blood was transfused through the head: when the blood was laden with CO_2 marked dyspnœa resulted; when arterial blood was transfused the normal respirations were restored.

While dyspnœa may be caused by the respiration of an atmosphere either deficient in O (" O-dyspnœa ") or containing an excess of CO_2 (" CO_2-dyspnœa "), the phenomena in the two cases are in certain respects different: When an animal breathes pure N, thus causing O-dyspnœa, the dyspnœa is characterized especially by frequent respiratory movements with vigorous inspirations, whereas if the atmosphere be rich in O and contain an excess of CO_2 the respirations are especially marked by a slower rate and by the depth and vigor of the expirations; O-dyspnœa continues for a long time before death ensues, and is more severe; in O-dyspnœa the absorption of O is diminished, but the excretion of CO_2 is practically unaffected; in O-dyspnœa the attendant rise of blood-pressure (p. 555) is more marked and lasting; in O-dyspnœa death is preceded by violent motor disturbances which are absent in CO_2-dyspnœa. Blood poor in O (O-dyspnœa) affects chiefly the inspiratory portion of the respiratory centre (p. 565), while blood rich in CO_2 (CO_2-dyspnœa) affects chiefly the expiratory portion; hence in the former the dyspnœa is manifest especially in an increase in the frequency of the respirations (hyperpnœa) and in the vigor of the inspirations, while in the latter it is manifest in a lessened rate, strong expirations, and expiratory pauses.

The marked increase in the depth of the respiratory movements in CO_2-dyspnœa is not solely due to the direct action of CO_2 upon the respiratory centre, for Gad and Zagari[2] have shown that CO_2 in abundance in inspired air acts upon the terminations of the sensory nerves of the larger bronchi and thus reflexly excites the respiratory centre. In a research on dogs these observers opened the trachea and passed glass tubes through the trachea and the larger bronchi to the smaller bronchi. Before the tubes were inserted the inhalation of CO_2 caused a considerable deepening of the respiratory move-

[1] *Bull. Acad. Roy. Méd. Belgique*, vol. 13, pp. 417–421.
[2] *DuBois-Reymond's Archiv f. Physiologie*, 1890, p. 588.

ments, but after the insertion of the tubes, by means of which the gas was carried directly to the smaller bronchi, the characteristic action of the CO_2 was no longer observed. From the results of these experiments we may conclude that the marked increase in the depth of the respiratory movements in CO_2-dyspnœa is due in part to the irritation of the sensory nerve-fibres of the mucous membrane of the larger bronchi.

The form of dyspnœa due to *muscular activity* is owing to the action upon the respiratory centre of certain substances which are formed in the muscles during contraction and are given to the blood. Muscular activity, as is well known, is accompanied by an increase in the rate and depth of the respiratory movements, and when the exercise is violent more or less marked dyspnœa may occur. Some physiologists have been led to the belief that the respiratory centre is connected directly or indirectly with the muscles by means of afferent nerve-fibres which convey impulses to the centre and thus excite it to activity; while others have regarded a diminution of O and an increase of CO_2 in the blood as the cause, the active muscles rapidly consuming the O in the blood and giving off CO_2 in great abundance; but Geppert and Zuntz[1] have clearly shown that neither of these theories is tenable, and that the respiratory excitation is due to products of muscular activity which are given to the blood and which act as powerful excitants to the respiratory centre. The precise nature of the bodies is unknown, but it is probable that they are of an acid character, for Lehmann[2] found that there was a distinct lessening of the alkalinity of the blood after muscular exercise. It is likely that the bodies are broken up in the system, because the results of Loewy's[3] investigations indicate that they are not removed by the kidneys.

Cardiac and *hemorrhagic* dyspnœas are chiefly due to the deficiency in the supply of O—the former, to the poor supply of blood due to the enfeebled action of the heart; and the latter, both to this and to the reduced quantity of blood (hæmoglobin). All circumstances which enfeeble the circulation or lessen the quantity of hæmoglobin therefore tend to cause dyspnœa; hence individuals with heart troubles or weakened by disease or with certain forms of anæmia are apt to suffer from dyspnœa upon the least exertion.

All circumstances which interfere with the interchange of O and the elimination of CO_2 in the lungs are favorable to the production of dyspnœa, as in pneumonia, pulmonary tuberculosis, growths of the larnyx, abdominal tumors, etc., especially so upon exertion.

Asphyxia is literally a state of pulselessness, but the term is now used to express a series of phenomena caused by the deprivation of air, as by placing an animal in a closed chamber of moderate size. These phenomena may be divided into three stages: the first is one of hyperpnœa; the second, of developing dyspnœa, and finally of convulsions; and the third, of collapse. During the first stage the inspiratory portion of the respiratory centre especially is excited, the respirations being increased in frequency and depth.

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[1] *Pflüger's Archiv f. Physiologie*, 1888, vol. 42, p. 189.   [2] *Ibid.*, p. 284.

[3] *Ibid.*, p. 281.

During the second stage the excitation of the expiratory portion of the respiratory centre is more intense than that of the inspiratory portion, so that the respirations become slow and deep, prolonged and convulsive, and the movements of inspiration are feeble and in striking contrast to the violent spasmodic expiratory efforts. During the third stage the dyspnœa is followed by general exhaustion; the respirations are shallow and occur at longer and longer intervals, the pupils become dilated, the motor reflexes disappear, consciousness is lost, the inspiratory muscles contract spasmodically with each inspiratory act, convulsive twitches are observed in the muscles of the extremities and elsewhere, gasping and snapping respiratory movements may be present, the legs are rigidly outstretched and the head and body are arched backward, feces and urine are usually voided, respiratory movements cease, and finally the heart stops beating. During these stages the circulation has undergone considerable disturbances. During the first and second stages the blood has been robbed of nearly all its O, the gums, lips, and skin become cyanosed, and, owing to the venous condition of the blood, the cardio-inhibitory centre has been decidedly excited, so that the heart's contractions are rendered less frequent; the vaso-constrictor centre for the same reason has also been excited, causing a constriction of the capillaries and an increase of blood-pressure. During the third stage these centres are depressed and finally are paralyzed.

If asphyxia be caused by ligating the trachea, the whole series of events covers a period of four to five minutes, the first stage lasting for about one minute, the second a little longer, and the third from two to three minutes. If asphyxia be produced gradually, as by placing an animal within a relatively large confined air-space, death may occur without the appearance of any motor disturbances (p. 544).

The heart usually continues beating feebly for several minutes after the cessation of respiration, so that by means of artificial respiration it is possible to restore the respiratory movements and other suspended functions. After death the blood is very dark, almost black. The arteries are almost if not entirely empty, while the veins and lungs are engorged.

Death from drowning occurs generally from the failure of respiration, occasionally from a cessation of the heart's contractions. It is more difficult to revive an animal asphyxiated in this way than one which, out of water, has simply been deprived of air for the same length of time. Dogs submerged for one and a half minutes can rarely be revived, but recovery can usually be accomplished after deprivation of air, out of water, for a period four to five times longer. After a person has been submerged for five minutes it is extremely difficult to effect resuscitation.

H. Artificial Respiration.

Effective methods for maintaining ventilation of the lungs are important alike to the experimenter and to the clinician. In the laboratory the usual method is to expose the trachea, insert a cannula (Fig. 139), and then periodically force air into the lungs by means of a pair of bellows or a pump. Some

of the forms of apparatus are very simple, while others are complicated. An ordinary pair of bellows does very well for short experiments, but for longer study, especially when it is necessary that the supply of air should be uniform, the bellows are operated by power. Some of these instruments are so constructed that air is alternately forced into and withdrawn from the lungs.

Periodical inflation of the lungs is termed *positive* ventilation; the periodical withdrawal of air from the lungs by suction is *negative* ventilation; and alternate inflation and suction is *compound* ventilation.
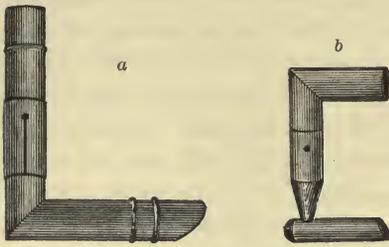
Fig. 139.—Cannulæ for dogs (*a*) and for cats and rabbits (*b*).

In practising artificial respiration we should imitate the normal rate and depth of the respiratory movements. Long-continued positive ventilation causes cerebral anæmia, a fall of blood-pressure, and decrease of bodily temperature.

In human beings it is not practicable, except under extraordinary circumstances, to inflate the lungs by the above methods, so that we are dependent upon such means as will enable us to expand and contract the thoracic cavity without resorting to the knife. One method is to place the individual on his back, the operator taking a position on his knees at the head, facing the feet. The lower ribs are grasped by both hands and the lower antero-lateral portions of the thorax are elevated, thus increasing the thoracic capacity, with a consequent drawing of air into the lungs; the ribs and the abdominal muscles are then pressed upon in imitation of expiration. These alternate movements are kept up as long as necessary.

The methods of Marshall Hall and Sylvester are now classic, and should be learned thoroughly by every physician. Marshall Hall's method is as follows: "After clearing the mouth and throat, place the patient on the face, raising and supporting the chest well on a folded coat or other article of dress. Turn the body very gently on the side and a little beyond, and then briskly on the face, back again, repeating these measures cautiously, efficiently, and perseveringly about fifteen times in the minute, or one every four or five seconds, occasionally varying the side. By placing the patient on the chest the weight of the body forces the air out; when turned on the side this pressure is removed and air enters the chest. On each occasion that the body is replaced on the face, make uniform but efficient pressure with brisk movements on the back, between and below the shoulder-blades or bones on each side, removing the pressure immediately before turning the body on the side. During the whole of the operations let one person attend solely to the movements of the head and of the arm placed under it."

The following is Sylvester's method: " Place the patient on the back, on a flat surface inclined a little upward from the feet; raise and support the head and shoulders on a small firm cushion or folded article of dress placed under

the shoulder-blades. Draw forward the patient's tongue, and keep it project-
ing beyond the lips; an elastic band over the tongue and under the chin will
answer this purpose, or a piece of string or tape may be tied around them, or
by raising the lower jaw the teeth may be made to retain the tongue in that
position. Remove all tight clothing from about the neck and chest, especially
the braces " . . . . " To imitate the movements of breathing : Standing at the
patient's head, grasp the arms just above the elbows, and draw the arms gently
and steadily upward above the head, and keep them stretched upward for two
seconds. By this means air is drawn into the lungs. Then turn down the
patient's arms, and press them gently and firmly for two seconds against the
sides of the chest. By this means air is pressed out of the lungs. Repeat
these measures alternately, deliberately, and perseveringly about fifteen times
in a minute, until a spontaneous effort to respire is perceived, immediately
upon which cease to imitate the movements of breathing, and proceed to
induce circulation and warmth."

The restoration of respiratory movements is usually facilitated by periodical
traction of the tongue, which acts as a reflex stimulus to the respiratory centre.

I. The Effects of the Respiratory Movements on the Circulation.

The respiratory movements are accompanied by marked changes in the cir-
culation. If a tracing be made of the blood-pressure and the pulse (Fig. 140),
and at the same time the inspiratory and expiratory movements be noted, it

IN. EX. IN. EX. IN. EX.
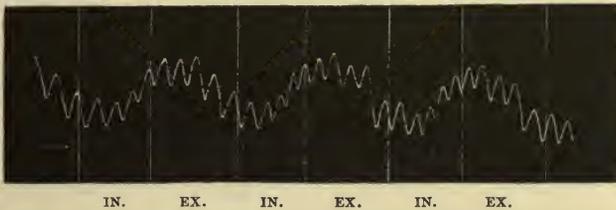
Fig. 140.—Blood-pressure and pulse tracing showing the changes during inspiration (IN.) and expi-
ration (EX.).

will be seen that the blood-pressure begins to rise shortly after the onset of
inspiration, commonly after a period occupied by one to three heart-beats, and
reaches a maximum after the lapse of a similar brief interval after the begin-
ning of expiration, when it begins to fall, reaching a minimum after the
beginning of the next inspiration. During inspiration the pulse-rate is more
frequent than during expiration and the character of the pulse-curve is some-
what different.

The Effects on Blood-pressure.—The changes in blood-pressure are
mechanical effects due to the actions of the respiratory movements. When it
is remembered that the lungs and the heart with their great blood-vessels are
placed within an air-tight cavity, that the lungs become inflated through the
aspiratory action of the muscles of inspiration, and that during inspiration

intrathoracic negative pressure is increased, it is easy to understand how the action which causes inflation of the lungs must affect in like manner such hollow elastic structures as the heart and the great blood-vessels, and thus influence the circulation. It is obvious, however, that this influence must make itself felt to a more marked degree upon the vessels than upon the heart, and upon the flaccid walls of the veins than upon the comparatively rigid walls of the arteries. Moreover, the effects upon the flow of blood through the vessels entering and leaving the thoracic cavity must be different : the inflow through the veins must be favored, and the outflow through the arteries hindered ; but it is upon the flaccid veins chiefly that the mechanical influences of inspiration are exerted. If the thoracic cavity be freely opened, movements of inspiration no longer cause an expansion of the lungs, nor is there a tendency to distend the heart and the large blood-vessels; if, however, in an intact animal the outlet of the thorax be restricted, as by pressure upon the trachea, the force of the inspiratory movement would make itself felt chiefly upon the heart and the vessels, and it is under such circumstances that the maximal influences of inspiration upon the circulation are observed. The lungs on the one hand and the heart and its large vessels on the other may be regarded as two sacs placed within a closed expansible cavity, the former having an outlet communicating with the external air, and the latter having inlets and outlets communicating with the extrathoracic blood-vessels, both being dilated when the thorax expands and constricted when it contracts. Moreover, the blood-vessels in the lungs may be compared to a system of delicate tubes placed within a closed distensible bag and communicating with tubes outside of the bag, simulating the communication of the venæ cavæ and the aorta with the extrathoracic vessels. When such a bag is distended the tubes also must be distended and their lumina in consequence be enlarged. The lungs in the same way, when expanded by the act of inspiration, are accompanied by a simultaneous dilatation of the intrapulmonary vessels, increasing their capacity, with the natural physical result of lessened resistance to the flow of blood.

During expiration negative intrathoracic pressure becomes less, so that there is a gradual return of the expanded intrathoracic vessels to that condition which existed at the beginning of inspiration ; at the same time the intrapulmonary vessels are not only subjected to the passive influence of the declining intrathoracic pressure, but are actively squeezed, as it were, between the air in the lungs on one side and the expiratory forces expelling the air on the other. Thus we have during expiration passive and active agents combining to bring about constriction of the intrapulmonary vessels.

The mechanical effects of the movements of respiration upon blood-pressure may be demonstrated by means of Hering's device (Fig. 141). The chamber A represents the thorax ; the rubber bottom B, the diaphragm ; C, the opening of the trachea ; E D, a tube leading from the thoracic cavity to the manometer I, by means of which intrathoracic pressure is measured ; G is a vessel containing water, colored blue in imitation of venous blood, communicating by means of a tube with an oblong flaccid bag F, in imitation of the heart and the intra-

thoracic vessels, and finally with the vessel H; v′ and v are valves in imitation of valves in the heart and pulmonary vein and aorta. If now the knob K which is fastened to the centre of the diaphragm be pulled down, rarefaction of the air within the chamber occurs, so that the greater external pressure forces air through the tube C into the two rubber bags (lungs); at the same time and for the same reason water is forced from the vessel G into F, which is distended. The diaphragm upon being released is drawn up in part by virtue of its own elasticity and in part by the negative pressure within the chamber. The rubber bags are emptied by their own natural elastic reaction. At the
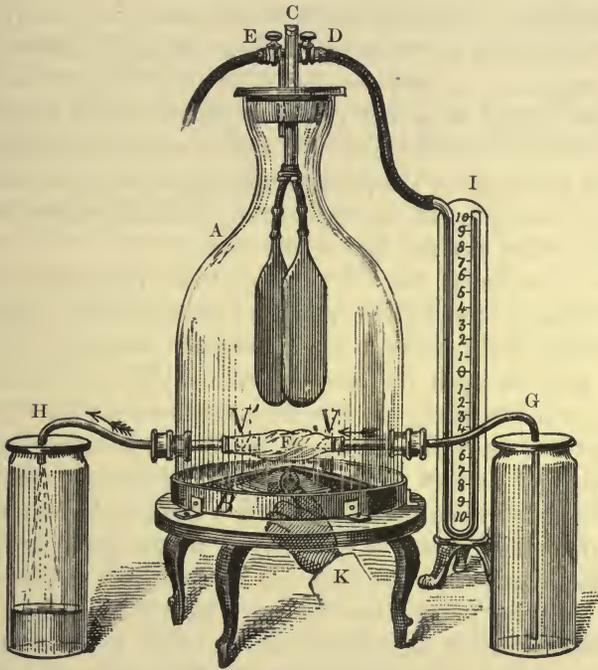
Fig. 141.—Hering's device to illustrate the influence of respiratory movements upon the circulation.

same time the distended bag F contracts on its contained fluid, forcing it into the vessel H, the valve v preventing a back-flow into G. The degree of force exerted by the traction on the diaphragm is read from the scale on the manometer.

This simple contrivance teaches us that during the entire phase of inspiration there is a condition of progressively increasing negative pressure within the thorax, and that not only is air aspirated into the lungs, but that blood is drawn into the large, flaccid venæ cavæ; and that during expiration there is a gradual diminution of negative pressure during which air is expelled from the lungs and blood from the expanded venæ cavæ.

The increased flow into the thoracic cavity during inspiration is favored in its progress through the pulmonary vessels by the attendant dilatation of the lung-capillaries and by the fact that the increased negative pressure affects the

thin-walled and slightly distended pulmonary veins more than the thick-walled and more distended pulmonary arteries, so that the "driving force" of the lung circulation, which is essentially the difference in pressure between the blood in the pulmonary arteries and that in the veins, is thereby increased during inspiration and the blood-current is driven with greater velocity. More blood thus being brought into the chest, and consequently to the heart, during inspiration, and less resistance being offered to the flow of the blood through the lungs, more blood must ultimately find its way to the left side of the heart, and consequently into the general circulation. If, therefore, the general capillary resistance in the systemic circulation remains the same, it is evident that an increased blood-supply to the left ventricle must cause the general blood-pressure to rise. That this rise does not become manifest immediately at the beginning of inspiration is doubtless owing to the filling of the flaccid and partially collapsed large veins and to the dilatation of the pulmonary capillaries. The continuance of the rise for a short time after the cessation of inspiration is due apparently to the partial emptying of the now distended lung-vessels, whereby, owing to the arrangement of the heart-valves, the excess of blood is forced toward the left side of the heart.

Besides the above factors, the flow of blood to the right side of the heart is favored by the pressure transmitted from the conjoint actions of the diaphragm and the abdominal walls through the abdominal viscera to the abdominal vessels. The pressure upon the arteries tends to drive the blood toward the lower extremities and to hinder the flow from the heart; in the veins, however, the flow toward the heart is encouraged, while that from the extremities is hindered. The rigid walls of the arteries protect them from being materially affected, but the flaccid veins are influenced to a marked degree; while, therefore, the flow from the left side of the heart is not materially interfered with, that through the veins toward the right side is appreciably facilitated, and thus the supply of blood to the heart is increased. The effects of these movements may be seen after section of the phrenic nerves, which causes paralysis of the diaphragm, when it will be noted that the blood-pressure curves are much reduced. This diminution is attributed to two causes—the enfeebled respiratory movements, which are now confined to the ribs and the sternum, and the absence of the pressure transmitted from the diaphragm through the abdominal organs to the veins. If in such an animal the abdomen be periodically compressed, in imitation of the effects produced by the contraction of the diaphragm, the respiratory curves may be restored to their normal height.

During expiration, since the conditions are reversed the effects also must be reversed. The increased negative intrathoracic pressure occasioned by inspiration now gives place to a gradual diminution, and with this a lessening of the aspiratory action due to the sub-atmospheric intrathoracic pressure; the blood-supply is further reduced because of the lessened amount of blood coming through the inferior vena cava; the abdominal veins, instead of being compressed and their contents forced chiefly toward the heart, are now being filled; finally, during the shrinkage of the lungs the intrapulmonary vessels

become constricted, and thus offer greater resistance to the flow from the right side of the heart through the lungs to the left side of the heart, and subsequently into the general circulation.

Another factor believed by some to be involved in the respiratory undulations in blood-pressure is a rhythmical excitation of the vaso-constrictor centre in the medulla oblongata, asserted to occur coincidently with the inspiratory discharge from the respiratory centre. This has, however, been disproved. Others have held that the blood-pressure changes are due to the pressure exerted by the expanding lungs upon the heart; while others contend that rhythmical alterations in the heart-beats are important. This latter factor is of importance in man and in the dog, in which there is a distinct increase in the rate of the heart-beat during inspiration, and co-operates in producing the general rise of pressure during inspiration.

The Effects on the Pulse.—During inspiration the pulse-rate is more rapid than during expiration. If we cut the pneumogastric nerves, it will be seen that, while the rate is increased as the result of the section, the difference during inspiration and expiration is abolished; on the other hand, if the thorax be widely opened, but the pneumogastric nerves are left intact, the inspiratory increase in the rate still occurs. This indicates that the cardio-inhibitory centre is either less active during inspiration or more active during expiration, and that there is an associated activity of the respiratory and cardio-inhibitory centres. Why this sympathy should exist between the respiratory and cardio-inhibitory centres we do not know, but it has been suggested that during expiration the blood reaching the centres is less highly arterialized than during the inspiratory phase, and that the cardiac centre is so sensitive to the difference as to be affected, and thus its activity is somewhat increased during the expiratory phase, with the consequent decrease in the pulse-rate.

During inspiration the pulse-rate is not only higher than during expiration, but the form of the pulse-wave is affected. The systolic, dicrotic, and secondary waves are smaller and the dicrotic notch is more pronounced, so that the dicrotic character of the curves is better marked.

The Effects of Obstruction of the Air-passages and of the Respiration of Rarefied and Compressed Air on the Circulation.—The blood-pressure undulations produced during quiet breathing become marked in proportion to the depth of the respiratory movements. Inspiration or expiration against extraordinary resistance—as after closing the mouth and nostrils, or respiring rarefied or compressed air—may materially modify the circulatory phenomena. When we make the most forcible inspiratory effort, the air passages being fully open, not only is there a full expansion of the lungs, but great diastolic distention of the heart and dilatation of the intrapulmonary and intrathoracic vessels; yet, notwithstanding that this powerful aspiratory action encourages the flow of an extraordinarily large amount of blood into the thoracic vessels, the heart-beats may be very small, because intrathoracic negative pressure is so great that the thin-walled auricles meet with great resistance while contracting; in consequence, then, of this forced inspiratory effort little

blood is driven through the lungs to the left auricle and by the left ventricle into the general circulation. If we make the greatest possible expiratory effort, and maintain the expiratory phase with air-passages open, the heart-beats are small, owing to the small amount of blood which flows through the venæ cavæ to the right auricle, and to the resistance offered by the constricted intrapulmonary vessels.

If, after a most powerful expiration, we close the mouth and nostrils and make a powerful inspiratory effort, the aspiratory effect of inspiration on the heart and the blood-vessels is manifest to its utmost degree : the heart and the vessels tend to undergo great dilatation, the blood-flow to the right auricle and ventricle is increased, the intrapulmonary vessels and the heart become engorged, and, owing to the powerful traction of the negative pressure upon the heart, especially upon the right auricle, very little blood is forced through the lungs to the left auricle and ventricle and subsequently into the general circulation, thus causing a fall of blood-pressure ; indeed, the heart-sounds and the pulse may disappear. If now we make the most forcible inspiratory effort, close the glottis, and make a powerful expiratory effort, not only is the air in the lungs subjected to high positive pressure, but the heart and the great vessels partake in the pressure-effects, the blood being forced from the pulmonic circulation into the left auricle, thence by the ventricle into the aorta, with the result of a temporary rise of blood-pressure. The pressure upon the intrathoracic veins is so great that the flow of blood into the chest is almost shut off, hence the veins outside the thorax become very much distended, as seen in the superficial veins of the neck, and the heart is pressed upon to such an extent that, together with the lessened supply of blood, the heart-sounds and the radial pulse may disappear and the blood-pressure falls.

The respiration into or from a spirometer (p. 535) containing rarefied or compressed air modifies the blood-pressure curves. Inspiration of rarefied air causes a greater rise of blood-pressure than when respiration occurs at normal pressure, while during expiration, although the blood-pressure falls, it may remain somewhat above the normal. The increase of pressure is due to the aspiratory effort required to draw the air into the lungs, which effort also makes itself felt to a more marked degree upon the heart and the intrathoracic and intrapulmonary vessels, thus increasing the blood-flow through the pulmonary circulation. During expiration air is aspirated from the lungs into the spirometer, tending to dilate the intrathoracic and intrapulmonary vessels and the heart and thus to aid the pulmonary circulation. After a time, however, there is a fall of blood-pressure on account both of the engorgement of the thoracic vessels and the accompanying depletion of the general circulation, and of the distention of the heart and interference with its contractions.

Inspiration of compressed air lessens the extent of, and may prevent, the inspiratory rise, or it may cause a fall. If, upon the respiration of compressed air, the pressure of the air be above that exerted by the elastic tension of the lungs, no effort of the inspiratory muscles is required, the chest being expanded by the pressure of the air. Therefore, instead of an increase of negative intra-

thoracic pressure, as in normal inspiration, there is a decrease, and negative intrathoracic pressure is replaced by positive pressure. As a result, the blood-vessels and the heart, instead of being dilated by an aspiratory action, are pressed upon, forcing the blood into the general circulation, and thus causing a transient rise of pressure, which is, however, succeeded by a fall due to obstruction to the flow of blood through the heart and the pulmonary vessels. Expiration into compressed air causes at first a transient increase of blood-pressure followed by a fall, the former being due to the forcing of some of the blood from the intrathoracic and intrapulmonary vessels into the general circulation, and the latter to obstruction to the blood-flow through the heart and the pulmonary circulation.

When individuals are exposed to compressed air, as in a pneumatic cabinet, or to rarefied air, as in ballooning, the effects on the circulation become of a very complex character, owing chiefly to the additional influences of the abnormal pressure upon the peripheral circulation; moreover, the effects of breathing against obstructions or of respiring rarefied or compressed air may be materially influenced by secondary effects resulting from excitation of the cardiac and vaso-motor mechanisms.

In *artificial respiration,* as ordinarily performed in the laboratory, air is periodically forced into the lungs by a pair of bellows or a pump, and is expelled from the lungs by the normal elastic and mechanical factors of expiration. When the lungs are inflated the pulmonary capillaries are subjected to opposing forces—the positive pressure of the air within the lungs on one hand, and the resistance of the thoracic walls on the other—so that the blood is squeezed out, thus momentarily increasing the blood-pressure, but subsequently retarding the current and consequently lowering the pressure. During expiration the pressure is removed and the blood-flow is encouraged; there is, therefore, a temporary fall during the filling of the pulmonary vessels, followed by a rise due to the removal of the obstruction. If the air is aspirated from the lungs, the rise of the pressure is augmented, owing to the further dilatation of the intrapulmonary capillaries; hence, in artificial respiration, during the inspiratory phase the blood-pressure curves are reversed, there being a primary transient rise followed by a fall, and during the expiratory phase a transient fall followed by a rise. In normal respiration the oscillations are due essentially to changes in negative intrathoracic pressure, while in artificial respiration, as above noted, they are due to changes in positive intrapulmonary pressure.

J. Special Respiratory Movements.

The rhythmical expansions and contractions of the thorax which we understand as respiratory movements have for their object the ventilation of the lungs. There are, however, other movements which possess certain respiratory characters, but which are for entirely different purposes, hence they are spoken of as special or modified respiratory movements. Some of these movements are purposeful in character, others are spasmodic; some are voluntary or in-

voluntary, or possess both volitional and involitional characteristics; some are peculiar to certain species, etc. Among such movements are coughing, hawking, sneezing, laughing, crying, sobbing, sighing, yawning, snoring, gargling, hiccough, neighing, braying, growling, etc.

In coughing a preliminary inspiration is followed by an expiration which is frequently interrupted, the glottis being partially closed at the time of the occurrence of each interruption, so that a series of characteristic sounds are caused. The air is forcibly ejected through the mouth, and thus foreign particles, such as mucus in the respiratory passages, may be expelled. Coughing may be either voluntary or reflex.

Hawking is somewhat similar to coughing. The glottis is, however, open during the expiratory act, and the expiration is continuous. The current of air is forced through the contracted passage between the root of the tongue and the soft palate. Hawking is a voluntary act.

In sneezing a deep inspiration is followed by a forcible expiratory blast directed through the nose; the glottis is open, and should the oral passage be open, which is not usually the case, a portion of the blast is forced through the mouth. Sneezing is usually a reflex act commonly excited by irritation of the fibres of the nasal branches of the fifth pair of cranial nerves. Peculiar sensations in the nose give us a premonition of sneezing; at such a time the act may be prevented by firmly pressing the finger upon the upper lip.

In laughing there is an inspiration followed, as in coughing, by a repeatedly-interrupted expiration during which the glottis is open and the vocal cords are thrown into vibration with each expiratory movement. The expirations are not as forcible as in coughing, the mouth is wide open, and the face has a characteristic expression due to the contraction of the muscles of expression.

Crying bears a close relationship to laughing—so much so that at times it is impossible to distinguish between the two; hence one may readily pass into the other, as frequently occurs in cases of hysteria and in young children. The chief differences between the two are in the rhythm and the facial expression. A secretion of tears is an accompaniment of crying, but not so of laughing, except during very hearty laughter. Crying normally is involuntary; laughing may be either voluntary or involuntary.

Sobbing, which is apt to follow a long period of crying, is characterized as being a series of spasmodic inspirations during each of which the glottis is partially closed, and the series is followed by a long, quiet expiration. This is usually involuntary, but may sometimes be arrested volitionally. In sighing there is a long inspiration attended by a peculiar plaintive sound. The mouth may be either closed or partially open. Sighing is usually voluntary.

Yawning has certain features like the preceding. There occurs a long, deep inspiration during which the mouth is stretched wide open, and there is usually a simultaneous strong contraction of certain of the muscles of the shoulders and the back; the glottis is wide open, and inspiration is accompanied by a peculiar sound; expiration is short. Yawning may be either voluntary or involuntary.

In snoring the mouth is open, and the inflow and outflow of air throws the uvula and the soft palate into vibration. The sound produced is more marked during inspiration, and may even be absent during expiration. It is more apt to occur when the individual is lying on his back than when in any other posture. Snoring is usually involuntary, but it may be volitional.

In gargling the fluid is held between the tongue and the soft palate and air is expired through it in the form of bubbles.

In hiccough there is a sudden inspiratory effort caused by a spasmodic twitch of the diaphragm and attended by a sudden closure of the glottis, so that the inspiratory movement is suddenly arrested, thus causing a characteristic sound. Hiccough is sometimes not only distressing, but may be even serious or fatal in its consequences. It is especially apt to occur in cases of gastric irritation, in certain forms of hysteria, in alcoholism, in uræmia, etc.

Besides the above special respiratory movements, others are observed in certain species of animals, such as whining, neighing, braying, roaring, bellowing, bawling, barking, purring, growling, etc.

Of all these modified respiratory movements, coughing possesses to the clinician the most interest, because it not only may express an abnormal condition of some portion of the lungs, trachea, or larynx, but may indicate irritation in even remote and entirely unassociated parts. Thus, coughing may be the result of irritation in the nose, ear, pharynx, stomach, liver, spleen, intestines, ovaries, testicle, uterus, or mamma. Coughs which are not dependent upon irritation of the larynx, trachea, or lungs are distinguished as sympathetic or reflex coughs. The term "reflex" is a bad one, however, inasmuch as all coughs are essentially or solely reflex.

K. The Nervous Mechanism of the Respiratory Movements.

The movements of respiration are carried on involuntarily and automatically—that is, they recur by virtue of the activity of a self-governing mechanism. Each respiratory act necessitates a finely co-ordinated adjustment of the contractions of a number of muscles, which adjustment is dependent upon the operations of a dominating or controlling nerve-centre located in the medulla oblongata, and known as the *respiratory centre.* Besides this centre, others of minor importance have been asserted to exist in certain parts of the cerebro-spinal axis; these centres are distinguished as *subsidiary* or *subordinate respiratory centres.* Connected with the respiratory centre are *afferent* and *efferent respiratory nerves.*

The Respiratory Centres.—After removal of all parts of the brain except the spinal bulb, rhythmical respiratory movements may still continue, but after destruction of the lower part of the bulb they at once cease. These facts indicate that the centre for these movements is in the medulla oblongata, and this conclusion is substantiated by the results of other experiments upon this region. According to the observations of Flourens, the respiratory centre is located in an area about 5 millimeters wide between the nuclei of the pneumogastric and spinal accessory nerves in the lower end of the calamus scriptorius.

When this region was destroyed he found that respiratory movements ceased and death ensued, consequently he termed it the *nœud vital*, or *vital knot*. The results of various investigations show, however, that Flourens' area, as well as certain other parts of the medulla oblongata that have been looked upon by others as being respiratory centres, are not such, but are largely or wholly collections of nerve-fibres which arise chiefly in the roots of the vagal, spinal accessory, glosso-pharyngeal, and trigeminal nerves, and which therefore are probably nerve-paths to and from the respiratory centre. Moreover, excitation of the *nœud vital* does not excite respiratory movements, but simply increases the tonicity of the diaphragm; nor is the destruction of the area always followed by a cessation of respiration. While the precise location of the centre is still in doubt, there is abundant evidence to justify the belief in its existence in the lower portion of the spinal bulb.

The centre is bilateral, one half being situated on each side of the median line, the two parts being intimately connected by commissural fibres, thus constituting physiologically a single centre. This union may be destroyed by section along the median line. Each half acts more or less independently of, although synchronously with, the other, and each is connected with the lungs and the muscles of respiration of the corresponding side. These facts are rendered manifest in the following observations: If a section be made in the median line so as to cut the commissural fibres, the respiratory movements on the two sides continue synchronously; if now the portion of the centre on the one side be destroyed, the respiratory movements on the corresponding side temporarily or permanently cease. If after section in the median line one pneumogastric nerve be divided, the sensory impulses conveyed from the lungs on the side of section to the corresponding half of the respiratory centre are prevented from reaching the centre, causing the movements of the respiratory muscles on the same side to be slower and the inspirations stronger as compared with those on the opposite side; if both pneumogastrics be divided, and the central end of one of the cut nerves be excited high in the neck by a strong current, the respiratory movements on the same side may be arrested, yet they may continue on the opposite side. These facts indicate that each half is in a measure independent of the other. The operations in the two parts are, however, intimately related, as shown by the fact that if the commissural fibres between the halves are intact, excitation or depression of one half is to a certain degree shared by the other. Thus, after section of one vagus not only are the respiratory movements less frequent and the inspirations stronger on the side of the section, but there is a corresponding condition on the opposite side; similarly, excitation of the central end of the cut nerve increases the respiratory rate both on the same and on the opposite side. Consequently, while there is more or less independence of the halves, the two are physiologically so intimately associated as to constitute a common or single centre.

Moreover, each of the halves may be supposed to consist of two distinct portions, one of which, upon excitation, gives rise to contraction of inspiratory muscles, the other to contraction of expiratory muscles; hence they are spoken

of as inspiratory and expiratory parts of the respiratory centre, or as *inspiratory* and *expiratory centres.* Moderate excitation of the inspiratory centre causes not only contraction of inspiratory muscles, but an increase in the respiratory rate; and if the irritation be sufficiently strong, there occurs a spasmodic arrest of the respiratory movements in the inspiratory phase. On the contrary, excitation of the expiratory centre causes contraction of expiratory muscles and diminishes the respiratory rate; powerful excitation of the same centre is followed by arrest of movements in the expiratory phase. The inspiratory portion may therefore be regarded not only as being specifically connected with inspiratory muscles, but in the sense of an *accelerator centre;* and the expiratory portion may be regarded as being similarly connected with expiratory muscles, and as being an *inhibitory centre.* When the two are conjointly excited the accelerator effect prevails, because under ordinary circumstances the accelerator element of the centre seems more excitable and potent than the inhibitory; therefore, when the centre as a whole is irritated, it manifests an accelerator character.

In addition to this centre, the existence of subsidiary centres is claimed, situated both in the brain and in the spinal cord. One centre has been located in the rabbit in the *tuber cinereum,* which has been named a polypnœic centre, because when excited the respirations are rendered extremely frequent. The sensitiveness of this centre is readily demonstrated by subjecting an animal to a high external temperature, when a marked increase of the respiratory rate follows; if now the tuber cinereum be destroyed, there occurs an immediate cesssation of the accelerated movements. Another area has been located in the *optic thalamus* in the floor of the third ventricle; this centre is believed to be excited by impulses carried by the nerves of sight and hearing, and when irritated causes an acceleration of the respiratory rate, and when strongly excited arrests respiration during the inspiratory phase; hence it is regarded as an inspiratory or accelerator centre. Another centre has been located in the *anterior pair of the corpora quadrigemina;* it causes expiratory and inhibitory effects, and may therefore be placed among the expiratory or inhibitory centres. An inspiratory or accelerator centre has been recorded as existing in the *posterior pair of the corpora quadrigemina* and the *pons Varolii.* The *nuclei of the trigemini* are also said to act as inspiratory or accelerator centres. Respiratory centres are likewise claimed to exist in the *brain-cortex.* It is very doubtful, however, whether or not these so-called subsidiary respiratory centres should be regarded as being of a specific character. In any event, we cannot suppose that these centres are capable of evoking directly respiratory movements. If they exist, they are probably connected with the medullary centre, through which they exert their influence on the respiratory movements.

The existence of a respiratory centre in the *spinal cord* is also doubtful. The chief reasons for the claim of its existence is that respiratory movements may for a time be observed after section of the cerebro-spinal axis at the junction of the spinal cord and bulb. In new-born animals after such section respiratory movements may continue for some time, strychnine rendering them

more pronounced. Again, animals in which respiration has been artificially maintained for a long time may, after section of the cord at the junction with the bulb, exhibit respiratory movements after artificial respiration has been suspended. The respiratory movements under these circumstances are, however, of a spasmodic character, and distinctly unlike the co-ordinated rhythmical movements observed in normal animals; the movements are rather of the nature of spasms simulating normal respirations.

The Rhythmic Activity of the Respiratory Centre.—The rhythmic sequence of the respiratory movements is due to periodic discharges from the respiratory centre. The cause of this periodicity is still obscure, but the fact that the rhythm continues after the combined section of the vagi and the glosso-pharyngeal nerves, of the spinal cord in the lower cervical region, of the posterior roots of the cervical spinal nerves, and of the spinal bulb from the parts above, indicates that the rhythm is inherent in the nerve-cells, and is not caused by external stimuli carried to the centre through afferent nerve-fibres. Loewy [1] has shown that under the above circumstances, when the centre is isolated from afferent nerve-impulses, the rhythmical activity of the centre is due to the blood, which, while acting as a continuous excitant, causes discontinuous or periodic discharges, so that, although we usually speak of the activity of the respiratory centre as being automatic—that is, not immediately dependent upon external stimuli—yet as a matter of fact the apparently automatic discharges are in reality due to the stimulation by the blood; the centre is therefore automatic only with reference to external nerve-stimulation.

The rhythm as well as the rate, force, and other characters of the discharges may be affected materially by the will and emotions; by the composition, supply, and temperature of the blood; and especially by certain afferent impulses, pre-eminently those originating in the pneumogastric nerves. As to the influence of the will and emotions, we are able, as is well known, to modify voluntarily to a certain extent the rhythm and other characters of the respirations, while the striking effect of emotions upon respiratory movements is a matter of almost daily observation. The importance of the composition of the blood is manifested by the marked effect upon the respirations when the blood is deficient in O, when it contains an excess of CO_2, and during muscular activity, when in the blood there is a relative abundance of certain products resulting from muscular metabolism. If the blood-supply to the centre is diminished, as after severe hemorrhage or after clamping the aorta so as to interfere with the cerebral circulation, the respirations are less frequent and the rhythm is affected, the form of breathing having a Cheyne-Stokes character (p. 532); conversely, an increase in the blood-supply causes an increase in the rate. An increase or decrease in the temperature of the blood induces corresponding changes in the rate; thus, in fever the frequency of the movements increases almost *pari passu* with the augmentation of temperature, while if the temperature of the blood be reduced by applying ice to the carotids, the rate is lessened.

[1] *Pflüger's Archiv f. Physiologie*, 1889, vol. xlii. pp. 245–281.

Afferent impulses exercise an important, and practically a continuous, influence. After section of one pneumogastric nerve the respirations are somewhat less frequent; after section of both nerves the respirations become considerably less frequent and deeper and otherwise changed. If we stimulate the central end of one of these cut nerves below the origin of the laryngeal branches by a current of electricity of moderate intensity, the respiratory rate may be increased, and we may be able to restore, or even exceed, the normal frequency. The fact that section of these nerves is followed by a diminution of the rate and that excitation of the central end of the cut nerve causes an increase leads us to believe that the pneumogastric nerves are continually conveying impulses from the lungs to the respiratory centre, which impulses in some way increase the number of discharges, and thus the respiratory rate. The centre may be excited or depressed by excitation of the cutaneous nerves and the sensory nerves in general; thus, external heat accelerates, while a dash of cold water may either accelerate or inhibit, respiratory movements. Excitation of the glosso-pharyngeal nerves inhibits the respirations. Such inhibition occurs during deglutition to avoid the risk of introducing foreign bodies into the larynx. Similar respiratory inhibition may be induced by excitation of the superior laryngeal nerves, when, if the degree of irritation be sufficiently strong, complete arrest of the respiratory movements may occur. Strong irritation of the olfactory nerves and of the fibres of the trigemini distributed to the nasal chambers excites expiration and may be followed by complete inhibition of the respiratory movements; strong irritation of the optic and auditory nerves excites inspiratory activity; and irritation of the sciatic nerve causes an increase of the rate, and may or may not affect the depth of breathing.

The study of the rhythmic activity of the respiratory centre is further complicated by the fact that there is not only a rhythmic sequence of the respirations, but a rhythmic alternation of inspiratory and expiratory movements. While it is true that in ordinary quiet expiration but little of the muscular element is present, yet forced expiration is a well-defined co-ordinated muscular act. The mechanism whereby this alternation is brought about is not understood. Some believe that the pneumogastric nerves contain both inspiratory and expiratory fibres which are connected with corresponding parts of the respiratory centre and alternately convey their respective impulses to the centre, inspiratory impulses being excited during expiration and expiratory impulses during inspiration (p. 505). These impulses are, however, not indispensable to the alternation of inspiration and expiration, because these acts follow each other regularly, even after the isolation of the respiratory centre from the lungs by section of the pneumogastric nerves.

Thus we may conclude that the rhythmical discharges from the centre are due primarily to an inherent property of periodic activity of the nerve-cells constituting the respiratory centre and maintained by the blood, and that the rhythm, rate, and other characters of these discharges may be affected by the will and the emotions, by the composition, supply, and temperature of the blood, and by various afferent impulses. The chief factors are, under ordi-

nary circumstances, the quantities of O and CO_2 in the blood, and the impulses conveyed from the lungs by the fibres of the pneumogastric nerves.

The Afferent Respiratory Nerves.—The chief of these nerves are the *pneumogastric, glosso-pharyngeal, trigeminal,* and *cutaneous nerves.* The important part taken by them in the regulation of the respiratory movements has frequently been alluded to in connection with the respiratory centres. Their functions, however, are of sufficient importance to demand special and detailed consideration.

The *pneumogastric nerves* are pre-eminently the most important. Their functions may be studied by comparing the phenomena before and after section of one or of both nerves, and from the results following excitation by stimuli of varying quality and strength under normal and abnormal conditions.

Section of *one* pneumogastric may be without effect or be followed by a transitory, slight diminution of the respiratory rate; by slower and deeper movements; by stronger, deeper, and longer inspirations; by unaltered or longer or shorter expirations; and probably by active expirations. These effects are transient, and the normal respiratory movements are usually restored within a half hour. *Section* of *both* nerves is sooner or later followed by a diminution of the respiratory rate; by slow, deep, powerful inspirations; by active expiration; and by a pause between expiration and inspiration. The immediate results are variable unless certain precautions are taken to prevent irritation of the central ends of the cut nerves. If the ends are allowed to fall back into the wound, the respirations may become irregular; or they may be less frequent, with weakened inspirations, spasmodic expirations, and prolonged expiratory pauses. The explanation of these variable results is found in the fact that the expiratory fibres are more sensitive to *very weak* stimulus than the inspiratory fibres, and that the mechanical irritation caused by the section, and the excitation due to the electric current in the cut ends of the nerves that is established when the central end of the nerve is replaced in the wound, excite expiratory impulses and cause expiratory phenomena; if the irritation be stronger, both inspiratory and expiratory impulses are excited, thus causing uncertain results, varying as one or the other is the stronger. If irritation be prevented, section is at once followed by typical slow, deep respirations.

Stimulation of the *central end* of the cut vagus, the other nerve being intact, is followed by variable results dependent upon the character of the stimulus. Chemical stimuli, such as a solution of sodium carbonate, excite the expiratory fibres; mechanical stimuli, the inspiratory fibres; electrical stimuli, expiratory or inspiratory fibres or both, according to the strength of the current. Single induction shocks are without effect, but a tetanizing current is very effective. Should that current which will elicit the least response be used, the breathing is rendered less frequent, the inspirations are weakened, and the expirations may be active and lengthened; in other words, there are present the same phenomena which often immediately follow section of both nerves when the cut ends are allowed to fall back into the wound and

thus establish an exciting electric current which affects expiratory fibres. If the strength of the current be increased, these effects give place to those of an opposite character, the respirations becoming more frequent and the inspirations more marked in depth and force, the explanation of this difference being that the stronger current has also excited inspiratory fibres, so that now both expiratory and inspiratory impulses are generated, but the latter, being more potent in their influences, cause acceleration of the rate and accentuated inspirations. The effects following stimulation of the central end of the cut vagus by a current of moderate strength are best observed after both nerves have been divided and when there exist slow, deep, powerful respirations. Under such circumstances stimulation of the central end of one of the vagi is followed at once by an increase in the respiratory rate and a return of the general characters of the inspiratory and expiratory phases toward the normal; and if the degree of excitation be properly adjusted, the normal rate and normal character of breathing may be restored. Still stronger excitation further accelerates the rate, causing the respiratory acts to follow each other with such frequency that inspiration begins before the expiratory act (relaxation of the inspiratory muscles) has been completed. The inspiratory muscles are therefore never completely relaxed. With a further increase of stimulus the expiratory relaxation becomes less and less, until finally the respirations are brought to a standstill in the inspiratory phase, the inspiratory muscles being in tetanus.

If the nerves be fatigued from over-excitation or if the animal be thoroughly chloralized, stimulation of the central end of the cut nerve by a strong current is no longer followed by inspiratory stimulation, but is followed by expiratory stimulation (the inspirations being shortened and weakened, the expirations prolonged and spasmodic) and by long pauses between expiration and inspiration. If the excitation be sufficiently strong, arrest of respiration occurs in the expiratory phase.

It will be observed from the above results that electrical irritation of the central end of the cut pneumogastric may be followed by effects of an opposite character, extremely weak irritation causing expiratory stimulation (weaker and shorter inspirations, prolonged and active expirations, expiratory pauses, and diminished respiratory rate); whereas moderate irritation causes inspiratory stimulation (stronger and deeper inspirations and increased respiratory rate). These diverse results are explained by the fact that these nerves contain two kinds of fibres having opposite functions: fibres of one kind convey impulses which affect the expiratory centre; those of the other kind convey impulses which affect the inspiratory centre. The former are more susceptible to weak electrical stimulation, and thus their presence may be elicited by the weakest stimulus capable of causing any response. At the same time they are less readily exhausted, so that if the vagi be subjected to prolonged stimulation by a strong current, the inspiratory fibres are exhausted before the expiratory fibres. For moderate and strong currents the inspiratory fibres are affected to a greater degree than the expiratory fibres, therefore inspiratory stimulation predominates.

Both sets of fibres convey impulses which have their origin essentially in the peripheries of the pneumogastric nerves in the lungs; but expiratory impulses may arise in the fibres of the superior and inferior laryngeal nerves, especially in the former. The impulses which arise in the lungs are under ordinary circumstances produced mechanically by the movements of the lungs, although it is believed by some that the composition of the gases in the alveoli is an important factor. According to the latter view, when the lungs are in the expiratory phase the accummulation of CO_2 in the air-cells excites the peripheries of the inspiratory fibres, thus giving rise to impulses which are carried to the inspiratory portion of the respiratory centre, and exciting inspiration; whereas the stretching of the lungs during inspiration is held to excite the peripheries of the expiratory fibres, generating impulses which are conveyed to the expiratory portion of the expiratory centre, causing expiration. There is, however, no sufficient evidence to lead us to believe that the presence of CO_2 in normal percentages influences in any way either set of fibres. On the contrary, the mechanical effects of the movements of the lungs are of great importance, as is apparent from the fact that inflation excites active expiration, whereas aspiration or collapse excites inspiration; moreover, if the movements of one lung be prevented by occlusion of the bronchi or by free opening of the pleural sac, the effects are the same as though the vagus of the same side were cut; if now the other nerve be severed, the results are the same as when both nerves are cut. The movements of the lungs therefore generate alternate inspiratory and expiratory impulses, collapse causing inspiratory impulses, and expansion causing expiratory impulses. The inspiratory impulses, however, not only excite inspiration, but concurrently limit the duration of expiration; while the expiratory impulses excite expiration and concurrently limit inspiration.

Excitation of the *superior laryngeal nerve* causes expiratory stimulation, and there may occur respiratory arrest in the expiratory phase. These fibres are extremely sensitive; and they are of considerable physiological importance, as is illustrated by the fact that the entrance of foreign bodies into the larynx during deglutition causes an immediate arrest of inspiration, and even a forced, spasmodic expiration. The foreign particles, coming in contact with the keenly sensitive fibres of these nerves, generate impulses which arrest inspiration, thus being prevented from being carried to the lungs.

The fibres of the *glosso-pharyngeal nerves* act similarly. Their excitation is followed by an arrest of respiration which lasts for a period equal to that occupied by about three of the preceding respiratory acts. The value of such an inhibitory influence is obvious: During swallowing breathing is arrested, evidently for the purpose of preventing the aspiration of food and drink into the larynx. This act is purely reflex, and is due to the excitation of fibres of these nerves by the fluid or the bolus of food after the act of deglutition has begun. Such impulses flow to the respiratory centre, immediately arresting the inspiratory discharge in whatever phase the inspiratory movement may

happen to be. When swallowing has been accomplished the inhibitory influence is removed and respiration is resumed.

The inhalation of irritating gases may cause respiratory arrest by exciting either the sensory fibres of the *trigeminal nerves* in the nose or the pneumogastric fibres in the larynx and lungs. Some gases affect the former, some the latter, others both. In the rabbit, for example, the introduction of tobacco-smoke into the lungs through a tracheal opening produces no effect upon the respirations, but if injected into the nose respiration is at once arrested. When ammonia is similarly introduced into the lungs the respirations may be either accelerated or diminished, and may be arrested in the inspiratory or the expiratory phase, but when drawn into the nose expiratory arrest follows. Some irritating gases arrest respiration in the inspiratory phase, others in the expiratory phase. Odorous gases which are powerful and disagreeable may similarly cause arrest by acting upon the *olfactory nerves.* Excitation of the *splanchnic nerves* causes expiratory arrest; stimulation of the *sciatic* and *sensory nerves in general* usually increases the number of respirations, yet under certain circumstances it may cause a decrease and final arrest during expiration.

Stimulation of the *cutaneous nerves,* as by a cold douche, slapping, etc., causes primarily a tendency to an increase in the number and depth of the respirations, but finally causes cessation in the expiratory phase. It is stated that excitation of these nerves is more effective in causing respiratory movements than irritation of the vagi. The influence of external heat is very powerful, and is perhaps the most potent means, under ordinary circumstances, of exciting the respiratory centre. The respiratory movements caused by cutaneous irritation, are, however, of the character of reflex spasms rather than of normal movements, and when the excitation is sufficiently strong the movements may be distinctly convulsive.

Finally, afferent (intercentral) fibres connect the *brain-cortex,* and probably the ganglia at the base of the brain, with the respiratory centres.

The Efferent Respiratory Nerves.—During ordinary respiration the only efferent or motor nerves necessarily involved are the *phrenics,* and certain other of the *spinal nerves,* and the *pneumogastrics.* Section of one phrenic nerve causes paralysis of the corresponding side of the diaphragm; section of both phrenics is followed by paralysis of the entire diaphragm. So important are these nerves in respiration that in most cases after section death occurs from asphyxia within several hours. In such cases not only is the work of inspiration thrown upon the other inspiratory muscles, but the effectiveness of the latter is greatly compromised by the relaxed condition of the diaphragm, which permits of its being drawn into the thoracic cavity with each inspiration, thus hindering the expansion of the lungs. If section be made of the spinal cord just below the exit of the fifth cervical nerve, costal movements cease, but diaphragmatic contractions continue. The level of the section is just below the origin of the roots of the phrenics, so that the motor fibres for the diaphragm are left intact, but the motor impulses which would have gone out to other inspiratory muscles

through the spinal nerves below the point of section are cut off. If the cord be cut just below the medulla oblongata or above the origin of the phrenics, both costal and diaphragmatic movements immediately or very soon cease, but respiratory movements may continue in the larynx, and when dyspnœa occurs they may be observed in the muscles of the face, neck, and mouth. In rare cases, after section at the junction of the medulla oblongata and the spinal cord, respiratory movements may continue in the thorax and the abdomen, but these instances are exceptional and the movements are of the nature of reflex spasms.

During each respiratory act there flow to the larynx impulses which open the glottis during inspiration. The pathway of these impulses is through the laryngeal branches of the vagi, almost solely through the recurrent or inferior laryngeal nerves. (See section on the Physiology of the Voice.) If the pneumogastrics are cut above the origin of these branches, respiratory movements in the larynx cease, and, owing to the paralysis of the laryngeal muscles, the vocal cords are flaccid, the glottis is no longer widened, and thus great resistance is offered to the inflow of air, causing difficulty during inspiration.

During forced breathing, besides the above nerves a number of others may be involved, especially the *spinal nerves*, which supply the extraordinary respiratory muscles of the chest, abdomen, pelvis, and vertebral column, and the *facial*, *hypoglossal*, and *spinal accessory* nerves.

L. The Condition of the Respiratory Centre in the Fetus.

During intra-uterine life the child receives O from and gives CO_2 to the blood of the mother. No attempt is made by the child to breathe, because the centre is in an apnœic condition, due to a low condition of irritability and to the relatively large amount of O in the blood. The fetal blood contains a larger percentage of hæmoglobin than the blood of the mother; Quinquaud has shown that the fetal blood has a larger respiratory capacity than adult's blood; and Regnard and Dubois have proven the same to be true of the calf and the cow. Were it not for these two conditions, the child would continually attempt to breathe. While such efforts do not occur under normal circumstances, they may be present if we interfere in any way with the supply of oxygen, as by pressure upon the umbilical vessels. The child has been seen to make respiratory efforts while within the intact fetal membranes. It seems evident, therefore, that all that is necessary to excite the respiratory centre to activity is a venous condition of the blood. *In utero*, and as long as the child is bathed in the amniotic fluid, respiratory movements cannot be carried on even though the respiratory centre be excited to activity, the reason being that with the first movement of inspiration amniotic fluid is drawn into the nasal chamber; the fluid acts as a powerful excitant to the sensory fibres of the mucous membrane, thus causing inhibitory respiratory impulses. From this fact we learn the practical application that it is desirable immediately after birth of a child, if spontaneous respirations do not immediately and effectively occur, to carefully remove mucus or other matter from the nose, so that the inhibitory influences generated by nasal irritation shall be discontinued.

When the exchange of O and CO_2 is interfered with for a long period, as in cases of prolonged labor, the respiratory centre may become so depressed that spontaneous respirations do not occur upon the birth of the child. In such a case respirations may usually be initiated by irritation of the skin, as by slapping, sprinkling with iced water, etc. Respirations may also be carried on successfully by artificial means (see p. 553).

In utero the lungs are devoid of air; the sides of the alveoli and of the small air-passages are in apposition, although the lungs completely fill the compressed thoracic cavity. During the first inspiration comparatively little air is taken into the lungs, because of the force necessary to overcome the adhesion of the sides of the alveoli and of the smaller air-tubes, but as one inspiration follows another inflation increases more and more until full distention is accomplished. The vigorous crying which so generally occurs immediately after birth doubtless is of value in facilitating this expansion. If once the lungs have been filled with air, they are never completely emptied of it, either by volitional effort or by collapse after excision.

M. The Innervation of the Lungs.

The nerves of the lungs are derived from the *pneumogastrics*, the *sympathetics*, and the *upper dorsal nerves*. Scattered along the paths of distribution of these fibres are many small *ganglia*.

The Pneumogastric Nerves.—The pulmonary branches of the pneumogastric nerves contain not only fibres which convey impulses that affect the general characters of the respiratory movements, but other fibres that are of great importance to the respiratory mechanism. Setting aside the effects on the respiratory movements following section and stimulation of one or of both vagi, there are observed phenomena which are of an entirely different character, and which are due to excitation or paralysis of certain other specific nerve-fibres. Among these fibres are efferent and afferent *broncho-constrictors* and *broncho-dilators*. Roy and Brown[1] found in investigations upon dogs that stimulation of one vagus caused constriction of the bronchi in both lungs; section of one vagus was followed by expansion of the bronchi in the corresponding lung, which expansion was sometimes preceded by a slight contraction owing to the temporary irritation caused by the section; stimulation of the peripheral end of the cut nerve caused a contraction of the bronchi in both lungs; stimulation of the central end of the cut nerve was followed by a contraction of the bronchi in both lungs, but not so marked as when the peripheral end was stimulated; stimulation of sensory nerves other than the vagus rarely, and then only to a slight extent, caused contraction; atropine paralyzed the constrictor fibres; nicotine in small doses had a powerful expansive effect on the bronchi; after etherization stimulation of either the central or the peripheral end of the cut pneumogastric nerve was often followed by broncho-dilata-

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[1] *Journal of Physiology*, vol. 6, 1885 (*Proceedings of the Physiological Society*, iii. p. xxi.); Einthoven, *Pflüger's Archiv für Physiologie*, 1892, vol. 51, p. 367; Sandeman, *Du Bois-Reymond's Archiv für Physiologie*, 1890, p. 252.

tion; asphyxia causes broncho-constriction, but not after section of the pneumogastric nerves; after section of both vagi it is impossible to cause reflex broncho-constriction or broncho-dilatation; the constriction of the bronchi may be so great as to reduce their calibres to one-half or one-third, or even more. The above results are very instructive, and show—(1) That broncho-constriction or broncho-dilatation can be obtained by stimulating the peripheral end of the vagus, and that these changes occur in the bronchi of both lungs when only one nerve is excited, thus proving that each nerve supplies both kinds of fibres to both lungs; (2) that the same results can be obtained by excitation of the central end of the cut nerve, thus showing that the pneumogastrics contain both afferent constrictor and afferent dilator fibres; (3) that reflex broncho-constriction and broncho-dilatation cannot be produced after section of the vagi, thus proving that all of the efferent fibres pass through the pneumogastrics; (4) that asphyxia and the inhalation of CO_2 cause broncho-constriction, but not after section of the vagi, thus indicating that under these circumstances the effects on the bronchi are reflex; (5) that certain poisons affect one or the other of these two sets of fibres.

The presence of *efferent vaso-motor* fibres in the vagi has been disproved by the results of experiments by Bradford and Dean,[1] and others. These observers have shown, however, that the vagi contain *afferent pressor* fibres, irritation of which is followed by constriction of the pulmonary vessels that may or may not be accompanied by constriction of the systemic vessels, the efferent fibres in this case reaching the lungs through the sympathetic nerves.

The existence of *trophic* fibres is generally admitted. After section of one pneumogastric nutritive changes immediately begin in the lung of the corresponding side, which changes are manifest in the appearance of inflammation in the middle and lower lobes. Section of both nerves is followed by inflammation in the middle and lower lobes of both lungs.

The vagi contain *sensory* fibres for the larynx, trachea, and lungs, after section of which fibres there is an absolute loss of sensibility in these parts.

It is probable that the vagi contain *secretory* fibres for the mucous glands.

Thus we find that the pneumogastric nerves supply the lungs with (1) afferent *inspiratory* and *expiratory* fibres; (2) afferent and efferent *broncho-constrictor* and *broncho-dilator* fibres; (3) afferent *pressor* fibres; (4) general *sensory* fibres; (5) *trophic* fibres; (6) and probably *secretory* fibres for the mucous glands.

The Sympathetic Nerves.—The sympathetics supply *trophic* and efferent *vaso-motor* fibres. The efferent vaso-motor fibres pass from the spinal cord in the anterior roots of the second to the seventh dorsal nerve, inclusive, to join the sympathetics, thence through the first thoracic ganglia to the lungs.

The Ganglia.—Nothing is known of the functions of the ganglia.

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[1] *Journal of Physiology*, 1894, vol. 16, p. 70.

IX. ANIMAL HEAT.

A. BODILY TEMPERATURE.

Homothermous and Poikilothermous Animals.—Animal organisms are divided as regards bodily temperature into two classes, homothermous and poikilothermous. The temperature of homothermous (warm-blooded) animals is constant within narrow limits and is not materially affected by alterations of the temperature of the medium in which the organism lives. The temperature of poikilothermous (cold-blooded) animals normally ranges from a fraction of a degree to several degrees above that of the surrounding medium, and under ordinary circumstances rises and falls with corresponding changes of surrounding temperature. The old terms warm-blooded and cold-blooded imply that the difference between the two classes is one of absolute temperature, the former having a temperature higher than the latter, and although this is generally the case it is not necessarily so. For instance, Landois has recorded that a frog (cold-blooded) in water at a temperature of 20.6° C. had a temperature of about 20.7° C., and that when the water was at 41° C. his temperature rose to about 38° C., which is higher than the mean temperature of man (warm-blooded). The temperature of cold-blooded animals may, therefore, be higher than that of warm-blooded animals. The difference therefore is relative and not absolute, the chief distinguishing feature being that the temperature of homothermous animals is practically constant, while that of poikilothermous animals fluctuates with the temperature of the medium in which the organism exists. The class of homothermous animals includes mammals and birds; and that of poikilothermous animals, fish, reptiles, amphibia, and invertebrates.

Temperatures of Different Species of Animals.—The temperature of every animal varies in different parts of the organism, so that in making comparisons it is necessary that the observations be made in the same region of the body of the different individuals, and as far as possible under the same internal and external conditions. As a rule, rectal temperatures are preferable, and in making them it is especially desirable, in order to ensure practical accuracy, that the bulb of the thermometer be inserted well into the pelvis, and that it does not rest within a mass of fecal matter. The depth to which the bulb is inserted is also of importance, as shown by Finkler, who found in experiments on a guinea-pig that the temperature was 36.1° C. at a depth of 2.5 centimeters, 38.7° C. at 6 centimeters, and 38.9° C. at 9 centimeters. The following records of mean bodily temperature of various species have been derived from various sources, chiefly from the compilations of Gavarret:

Mammals.		Birds.		Reptiles and Fish.[1]	
	Centigrade.		Centigrade.		Centigrade.
Mouse	41.1°	Birds	44.03°	Frog	0.32–2.44°
Sheep	37.3–40.5°	Duck	42.50–43.90°	Snakes	2.5–12.0°
Ape	35.5–39.7°	Goose	41.7°	Fish	0.5–3.0°
Rabbit	39.6–40.0°	Gull	37.8°		
Guinea-pig	38.4–39.0°	Guinea	43.90°	Invertebrates.[1]	
Dog	37.4–39.6°	Turkey	42.70°	Crustacea	0.6°
Cat	38.3–38.9°	Sparrow	39.08–42.10°	Cephalopods	0.57°
Horse	36.8–37.5°	Chicken	43.0°	Medusæ	0.27°
Rat	38.8°	Crow	41.17°	Polyps	0.21°
Ox	37.5°			Molluscs	0.46°
Ass	36.95°				

The Temperature of the Different Regions of the Body.—The quantities of heat produced and dissipated by different parts of the economy vary, consequently there must continually be a transmission of heat from the warmer to the cooler parts to establish throughout the organism an equilibrium of temperature. Heat is distributed by direct conduction from part to part, but probably chiefly by the circulating blood and lymph. These means of distribution are, however, not sufficiently active to establish a uniform temperature. Thus we find that the internal parts of the body have a higher temperature than the external parts; that some internal organs are considerably warmer than others; that every organ is warmer when active than when at rest; that the temperature varies in different regions of the surface of the body, etc. The following figures by Kunkel[2] instance some of these differences, the temperature of the room being 20° C.:

	Centigrade.		Centigrade.
Forehead	34.1°–34.4°	Sternum	34.4°
Cheek under the zygoma	34.4°	Pectorales	34.7°
Tip of ear	28.8°	Right iliac fossa	34.4°
Back of hand	32.5°–33.2°	Left iliac fossa	34.6°
Hollow of the hand (closed)	34.8°–35.1°	Os sacrum	34.2°
Hollow of the hand (open)	34.4°–34.8°	Eleventh rib (back)	34.5°
Forearm	33.7°	Tuberosity of ischium	32.0°
Forearm (higher)	34.3°	Upper part of thigh	34.2°
		Calf	33.6°

The temperature of the skin is higher over an artery than at some distance from it; it is higher over muscle than over sinew; it is higher over an organ in activity than when at rest; it is higher in the frontal than in the parietal region of the head, and on the left side of the head than on the right, etc.

Temperature observations are usually made in the rectum, in the mouth under the tongue, in the axilla, and in the vagina, the rectum being preferable, although in the human being the temperature is usually obtained in the mouth and axilla. In the same individual when records are taken simultaneously in all four regions appreciable differences will be noted. The temperature in the axilla is, according to Hunter 37.2° C., to Davy 37.3° C., to Wunderlich 36.5° to 37.25° C. (mean 37.1° C.), to Liebermeister 36.89° C., to Jürgensen 37.2° C.,

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[1] Temperatures above that of the surrounding medium.

[2] *Zeitschrift für Biologie*, 1889, vol. 25, pp. 69–73.

and to Jaeger 37.3° C. The mean axillary temperature may be put down as being about 37.1° C. (98.8° F.), the normal limits being 36.25° to 37.5° C. (97.2° to 99.5° F.) The temperature in the mouth is about 0.2° to 0.5° C. higher than in the axilla, in the rectum from 0.3° to 1.5° C. higher, and in the vagina from 0.5° to 1.8° C. higher.

The temperature of different tissues varies. Davy, as results of observations on a fresh-killed sheep, gives the temperature of the brain as about 40° C.; of the left ventricle 41.67° C.; of the right ventricle 41.11° C.; of the liver 41.39° C.; of the rectum 40.56° C. According to Bernard, the liver is the warmest organ in the body, and then the following in the order named— brain, glands, muscles, and lungs.

The temperature of the blood varies considerably in different vessels. In the carotid it is from 0.5° to 2° C. higher than in the jugular vein; in the crural artery, from 0.75° to 1° C. higher than in the corresponding vein; in the right side of the heart about 0.2° C. higher than in the left; in the hepatic vein 0.6° C. higher than in the portal vein during the intervals of digestion, and as much as 1.5° to 2° C. or more during periods of digestion; the venous blood coming from internal organs is warmer than the arterial blood going to them, but the blood coming from the skin is cooler than that going to it; the blood coming from a muscle in a state of rest is about 0.2° C., and during activity as much as 0.6° to 0.7° C., warmer than that supplied to the muscle. The mean temperature of the blood as a whole is about 39° C. (102° F.); of venous blood about 1° C. (1.8° F.) lower than of arterial blood. The warmest blood in the body is that coming from the liver during the period of digestion; the coolest blood is that coming from the tips of the ears and nose and similarly exposed parts.

Conditions affecting Bodily Temperature.—The mean temperature of the body is subjected to variations which depend chiefly upon age, sex, constitution, the time of day, diet, activity, season and climate (surrounding temperature), the blood-supply, disease, drugs, the nervous system, etc.

The temperature of a new-born child (37.86° C.) is from 0.1° to 0.3° C. higher than that of the vagina of the mother; it falls about 1° C. during the first few hours after birth, and then rises within the next twenty-four hours to about 37.4° to 37.5° C. The mean temperature of an infant a day or two old is about 37.4° C. It very slowly sinks until full growth is attained, when the normal mean temperature of adult life is reached (37.1° C.), a standard which is maintained until about the age of forty-five or fifty, when it declines until about the age of seventy (36.8° C.), and then slowly rises and approaches in very old people (eighty to ninety years) the temperature of very young infants (37.4° C.). It is important to observe that during the early weeks of life the temperature may undergo considerable variations, and that it is readily affected by bathing, exposure, crying, pain, sleep, etc., and by many circumstances which have little or absolutely no influence upon the temperature of the adult.

The mean temperature of the female is said to be slightly lower than that

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of the male. In observations on children Sommer noted a difference of 0.05° C., and Fehling a difference of 0.33° C.

Individuals with vigorous constitutions have a somewhat higher temperature than those who are weak.

Records obtained by various European investigators indicate that the bodily temperature is subjected to regular diurnal variations. The limits of variation in health are from 1° to 2° C. The maximum temperature observed is usually from 5 to 8 P. M. (mean, about 7 P. M.); the minimum, from 2 to 6 A. M. (mean, about 4 A. M.). Carter's[1] experiments on rabbits, cats, and dogs show that rhythmical temperature-changes occur in these animals which agree with those noted by Jürgensen in man. This same rhythm is stated to occur during fasting, so that the ingestion and the digestion of food cannot be claimed to account for it; moreover, it is present in fever and not disturbed by muscular activity and by cold baths. If an individual works at night and sleeps during the day, thus reversing the prevailing custom, the temperature curve is reversed, the lowest temperature being noted in the evening and the highest in the morning.

Insufficient diet causes a lowering of the temperature; a liberal diet tends to cause a rise slightly above the normal mean, especially during forced feeding or when the food is particularly rich in fats and carbohydrates. There is a rise during digestion which is usually slight, but it may reach 0.2° or 0.3°, the increase being due chiefly to the activity of the intestinal muscles (see p. 540). Although considerably more heat is produced during the periods of digestion than during the intervals, the excess is dissipated almost as rapidly as it is formed, so that but little heat is permitted to accumulate and thus cause a rise of temperature. Hot drinks and solids tend to augment, and cold drinks and solids to lower bodily temperature. In the nursing child Demme found that the rectal temperature sinks during the first half-hour after taking food, then rises during the next sixty to ninety minutes to a point from 0.2° to 0.8° C. higher than the temperature before feeding, and falls again during the next thirty to sixty minutes.

All conditions which increase metabolic activity are favorable to an increase of temperature. Thus, during the activity of the brain, glands, muscles, etc., more heat is produced than when the tissues are at rest; indeed, so abundant is heat-production during severe muscular exercise that the temperature of the body may rise as much as 0.5° to 1.5° C. (1° to 2.7° F.). During sleep the temperature falls from 0.3° to 0.9° C. or more in young children.

During the summer the mean bodily temperature is from 0.1° to 0.3° C. higher than during the winter. In warm climates it is about 0.5° C. higher than in cold climates, but the difference is not due to race, since it is observed in individuals who have changed their habitations from one climate to another. Continued exposure to excessively high or low temperatures is inimical to life. Exposure in dry air at a temperature of 100° to 130° C. may cause the bodily temperature to increase as much as 1° to 2° C. within a few minutes,

[1] *Journal of Nervous and Mental Diseases*, 1890, vol. xvii. p. 782.

and the temperature may rise so rapidly as to cause fatal symptoms within ten or fifteen minutes. A hot moist air is far more oppressive and dangerous than hot dry air.

Baths exercise a potent influence on bodily temperature, hot baths increasing and cold baths decreasing it. The effect of a cold bath is less if it follows a hot bath. Thus Dill[1] found that his morning temperature varied from 33.7° to 36.6° C., after a hot bath (40°–41° C.) it rose, in one instance, as high as 39.5° C., and after a cold bath it remained at 37° C. When, however, the hot bath was omitted the cold bath reduced the temperature to 35.4° C. Baljakowski[2] has recorded some very interesting results which show that the local application of heat causes the bodily temperature to sink and the cutaneous temperature of the part experimented upon to rise. The experiments were conducted on young men, whose arms and legs were encased in hot sand at a temperature of 55° C. When the arm was used the axillary temperature sunk an average of 0.13° C. during the bath and subsequently 0.24° C., the corresponding records of average rectal temperature being 0.23° and 0.31° C. In case of the leg bath the corresponding records were axillary 0.06° and 0.32° C.; and rectal 0.21° and 0.25° C. The cutaneous temperature of the limb experimented upon increased materially, the average rise varying from 0.73° to 1.20° C., according to the part of the limb. Long-continued severe external cold may prove fatal, but this is not necessarily due to the effect on bodily temperature, for Milne-Edwards[3] has shown that rabbits die within five or six days when exposed to a temperature of −10° to −15° C., without the bodily temperature falling more than 1° C.

There is a general relationship between the frequency of the heart's beat and the bodily temperature, especially in fever. Bärensprung noted such a coincidence between the diurnal variations of the pulse and bodily temperature; and, in fever, Aiken found that for each increase of 0.55° C. (1° F.) above the mean normal temperature the pulse-rate was increased about ten beats per minute. But the variations in the two do not always correspond either quantitively or qualitatively. Liebermeister found in man that for a rise of each degree from 37° to 42° C. the increase in the pulse-rate was 12.6, 8.6, 8.7, 11.5, and 27.5 beats per minute respectively. Beljakowski's[4] experiments show that the bodily temperature may fall and the pulse-rate rise—in one set of experiments the rectal temperature falling on an average 0.23° C. and the pulse increasing on an average 6.85 beats per minute. After the local hot bath the temperature remained subnormal, and the heart-beats became less frequent, and finally were on an average from 2.7 to 3.1 beats per minute less than the normal rate.

More important, however, than the pulse-rate is the effect of the amount of blood supplied to any given part of the body. The mere lowering or raising of the arm is sufficient to alter the blood-supply to the part; thus Römer found that keeping the arm elevated for five minutes was sufficient to reduce

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[1] *British Medical Journal*, 1890, vol. i. p. 1136.

[2] *Vratch*, 1889, p. 436; *Provincial Medical Journal*, 1890, p. 113.

[3] *Comptes rendus de la Soc. de Biologie*, 1891, vol. 112, pp. 201-205.　　　　[4] *Loc. cit.*

the temperature of the hand 0.19° C., and that if the period was doubled the fall amounted to 0.38° C. Compression of the veins of the arm may diminish the temperature of the hand as much as 0.25° to 2.45° C., while compression of the brachial artery may cause a fall of 2.4° within fifteen minutes. A larger supply of blood to the cutaneous surface increases cutaneous temperature and tends to decrease internal temperature, while a lessened supply causes the opposite effects.

In abnormal conditions the temperature may be increased or decreased : in cholera, diabetes, and in the last stages of insanity, it may be lowered 6° or 8° C. or even more. In fever it is increased, usually ranging between 37.5° and 41.5° C. (99.4° and 106.7° F.), but in very rare cases it may reach 44° to 45° C. (111° to 113° F.) just before death. A temperature of 42.5° C. (108.5° F.) maintained for several hours is almost inevitably fatal. In frogs, the highest temperature consistent with life for any length of time is below 40° C. ; in birds, from 48° to 50° C., and in dogs, from 43° to 45° C. Exceptional cases are on record of people having survived extraordinarily high or low bodily temperature, Richet having reported one in which the temperature several times was 46° C. (114.8° F.), while Teale records an axillary temperature of 50° C. (122° F.) in an hysterical (?) woman. Fräntzel noted a temperature of 24.6° C. (76.2° F.) in a drunken man, and Kosürew a temperature of 26.5° C. (79.7° F.) in a man having a fractured skull.

Bodily temperature may be variously influenced by drugs and other substances, micro-organisms, etc. Some increase it, others decrease it, others are without any marked influence, while others exert primary and secondary actions. Among those which increase bodily temperature are cocain, atropin, strychnin, brucin, caffein, veratrin, etc., and, as shown by Krehl[1] and others, a large number of other organic substances and micro-organisms. Temperature is decreased by anæsthetics, morphin and other hypnotics, quinin, various antipyretics, large doses of alcohol, etc.

Among the most important of the conditions which affect bodily temperature are disturbances of the nervous system. Injury or irritation of almost any part of the nerve-centres and of certain nerves may give rise directly or indirectly to alterations of temperature, and there are some parts which are very sensitive in this respect, especially certain areas of the brain cortex, the striated bodies, the pons Varolii, the spinal bulb, and the cutaneous nerves. The results of injury or stimulation of these as well as of other parts will be considered later on (p. 600).

Temperature-regulation.—The fact that during life the organism is *continually* producing and losing heat, and that the bodily temperature of homothermous animal is maintained at an almost uniform standard, notwithstanding considerable mutations of surrounding temperature, renders it evident that there exists an important mechanism whereby the regulation of the relations between heat-production and heat-dissipation is effected. It must be evident that when the variations in heat-production and heat-dissipation balance, bodily

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[1] *Archiv für experimentelle Pathologie und Pharmakologie*, 1895, vol. 35, pp. 222–268.

temperature must remain unaltered, and that if the changes in one exceed those in the other the temperature rises or falls, depending upon whether more or less heat is produced than is dissipated. It does not follow that because heat-production is increased the bodily temperature must similarly be affected, since heat-dissipation may be increased to the same extent and thus effect a compensation. Therefore an alteration in heat-production or in heat-dissipation by no means implies that the temperature must be affected. Moreover, when the temperature is increased or diminished the change may be caused by various alterations in the quantities of heat produced or lost, singly or combined, and the temperature may remain constant even when both processes are materially affected. Thus, the temperature remains *constant* when both heat-production and heat-dissipation are normal, and when both are increased or decreased to the same extent. The temperature is *increased* when heat-production is normal and heat-dissipation diminished; when both heat-production and heat-dissipation are diminished, but when heat-production is diminished to a less extent than heat-dissipation; when heat-production is increased and heat-dissipation remains normal; when both heat-production and heat-dissipation are increased, but when heat-production is increased to a greater extent than heat-dissipation; and when heat-production is increased and heat-dissipation is diminished. The temperature is *diminished* when heat-production is normal and heat-dissipation is increased; when heat-production is diminished and heat-dissipation remains normal; when heat-production and heat-dissipation are diminished, but when heat-production is diminished to a greater extent than heat-dissipation; when heat-production is diminished and heat-dissipation is increased; and when both heat-dissipation and heat-production are increased, but when heat-production is increased to a less extent than heat-dissipation.

It is generally regarded by clinicians that bodily temperature varies directly with heat-production—that is, that a rise means increased production, and a fall diminished production; but the fallaciousness of such a conclusion must be apparent. It may, however, be accepted as a fact that in fever, as a rule, an increase of bodily temperature is a concomitant of increased heat-production, and diminished temperature of diminished heat-production; but it must also be observed that pyrexia, although generally due to increased heat-production, may also be due partly or wholly to diminished heat-dissipation. It is obvious, therefore, that temperature variations simply show that the balance between heat-production and heat-dissipation is disturbed, without positively indicating how the processes of heat-production and heat-dissipation are affected.

The mechanism concerned in the adjustment of the relations between heat-production and heat-dissipation will be considered under another heading (p. 602).

B. INCOME AND EXPENDITURE OF HEAT.

Broadly speaking, the source of animal heat is in the potential energy of organic food-stuffs—so little relatively being obtained from the heat of warm

food and drink and directly from external sources, such as the sun's rays, that these sources may be disregarded. This potential energy of food may be converted into heat *directly* or *indirectly ;* directly, as an immediate result of chemical decomposition ; and indirectly, by mechanical movements, such as muscular contraction, the flow of the blood, the friction of the joints, etc. About 90 per cent. of the heat of the organism results directly from chemical decompositions, and about 10 per cent. results indirectly from mechanical movements. The potential energy of the food is transformed into kinetic energy (heat and work) essentially by processes of oxidation. The energy-yielding food-stuffs enter the body in the form of proteids, fats, and carbohydrates. The proteid is oxidized into urea, CO_2, H_2O, and various extractives ; and the fats and carbohydrates are reduced to CO_2 and H_2O. During these oxidative processes, by which the potential energy of the molecules is transformed into kinetic energy, the total amount of energy evolved by the complete oxidation of a given amount of any substance is the same whether the processes are carried at once to the final stages, that is, to the final disintegration products, or whether they pass through an indefinite number of intermediate stages, provided that the final product or products are the same. In other words, the amount of heat evolved by the oxidation of 1 gram of proteid into urea, CO_2, and H_2O is the same when the molecule is oxidized immediately into these substances as when the decomposition is carried through a number of intermediate stages. Similarly 1 gram of carbon oxidized into CO_2, or 1 gram of H oxidized into H_2O, yields a definite amount of heat, 1 gram of C yielding 8080 calories (see p. 584 for definition of calorie), and 1 gram of H 34,460 calories ; 1 gram of proteid oxidized into CO_2 and H_2O yields 5778 calories ; 1 gram of fat oxidized into CO_2 and H_2O yields 9312 calories ; and 1 gram of carbohydrate oxidized into CO_2 and H_2O yields 4116 calories (see Potential Energy of Food, p. 302).

Income of Heat.—Since the energy-yielding food-stuffs are essentially proteids, fats, and carbohydrates, and composed of C, H, O, and N, and since the products of their disintegration are essentially urea, CO_2, and H_2O, the amount of energy yielded by the oxidation of the food-stuffs can readily be determined if we know the quantity and quality of the food and excreta. Since the energy of the organism is manifested essentially in the form of heat and work, and as under ordinary circumstances but a fraction of it is manifested as work, we may in making this estimate, as a matter of convenience, consider that the total available energy of the food appears in the form of heat.

The income of energy may be estimated by determining—(1) the quantity of oxygen consumed ; (2) the amounts of C and H that are oxidized in the body into CO_2 and H_2O ; (3) the quantity and quality of the food, and the energy yielded by the oxidation of the same substances outside the body when they are decomposed into the same residual products as appear in the body ; (4) the quantity of heat produced, by the aid of a calorimeter, the individual being kept quiet so that as little as possible of the energy expended appears as work.

The first two methods have fallen into disuse. According to the third method it is necessary that we know the kind and quantity of food ingested, the final products of disintegration, and the quantity of energy evolved by the oxidation of each of the food-stuffs to their normal residual substances. As the basis of these calculations we have the fact that during the complete oxidation of any given substance a definite amount of energy is given off, and that when the oxidation is but partial only a portion of energy is evolved, the proportion being in accordance with the stage of oxidation. The complete oxidation of 1 gram of proteid yields 5778 calories; of 1 gram of fat, 9312 calories; and of 1 gram of carbohydrate, 4116 calories (see Potential Energy of Food, p. 302). If these substances be completely oxidized in the body, the amount of energy evolved will be the same as though the oxidation occurred outside of the body, provided that the final products are the same in both cases. As far as fats and carbohydrates are concerned, we are justified in assuming that they are completely oxidized in the body into CO_2 and H_2O; but the proteids, as already pointed out, undergo only partial oxidation, each gram yielding about one-third of a gram of urea. The results of experiments show that each gram of urea contains potential energy equivalent to 2523 calories, and since each gram of proteid yields one-third of a gram of urea, representing 841 calories, each gram of proteid yields to the organism only 4937 calories. The available energy from the proteid would, therefore, be equivalent to the total amount of energy derivable from the complete oxidation of the proteid minus the amount represented in the urea. With these facts in view it is a simple matter to determine the total income of energy, should the diet be known. Thus, if the diet consists of 120 grams of proteids, 90 grams of fat, and 330 of carbohydrates, the absolute and available amounts of energy ingested are—

	Grams.		Calories.	Calories.
Proteids	120	×	5778	693,360
Fats	90	×	9312	837,080
Carbohydrates	330	×	4116	1,358,280
				2,888,720
Deduct the proteid energy in 40 grams of urea, $40 \times 2523 =$				100,920
Total daily heat-production				2,787,800

This is assuming that the entire quantity of proteids, fats, and carbohydrates is digested, absorbed and ultimately broken down into CO_2, H_2O, and urea. This assumption, however, is not justified by facts, since we know, for instance, that more or less food escapes digestion. In practice, therefore, it is necessary to ascertain from the excreta of the animal (see section on Nutrition) just how much of the ingested food has been absorbed and completely or partially destroyed in the body.

Calorimetric investigations also afford us indirect information as to the *income* of heat by showing the quantities of heat produced and dissipated. Such data are of much value, since it is evident that should the energy of the body be maintained in a condition of equilibrium from day to day, and should the energy resulting from the transformation of potential energy be manifested

solely in the form of heat, it follows that the mean daily heat-production and income of available energy must balance. But it cannot be considered that this balance is maintained at a constant standard from hour to hour, nor from day to day; on the contrary, the fluctuations are undoubtedly considerable, as is obvious by the fact that we are continually expending energy and only periodically (at meal-times) acquiring energy. During fasting there is absolutely no income of energy, yet the output of heat may be subnormal, normal, or hypernormal; on the other hand, if an excess of energy be ingested, as in excessive eating, it is not by any means implied that there is a similar excess in heat-production, because some of the food ingested may be lost as undigested food or as partially oxidized excrementitious matters, or may be stored in the body in the form of carbohydrate, fat, or proteid; nor does an excess of heat-production imply an excess of income of energy, because the stored-up energy may be drawn upon. (For results of the calorimetric method see p. 589.) The results of the various methods are in close accord, and indicate that in the adult the total income of available energy is about 2,500,000 calories.

Expenditure of Heat.—Assuming that the energy of the organism is expended in the form of heat, and that the total income of available energy is 2,500,000 calories, it has been estimated by Vierordt that about—

1.8 per cent. is lost in the urine and feces						47,500 calories.
3.5 " " " expired air						84,500 "
7.2 " " " evaporation of water from the lungs						182,120 "
14.5 " " " " " " skin .						364,120 "
73.0 " " " radiation and conduction from skin						1,791,820 "
						2,500,000 calories.

Therefore, about 87.5 per cent. is lost by the skin, 10.7 per cent. by the lungs, and 1.8 per cent. in the urine and feces.

C. Heat-production and Heat-dissipation.

Calorimetry.—The *intensity* of heat of any substance is measured by means of a thermometer or thermopile; the *quantity* of heat present is estimated by the weight, the specific heat, and the mean temperature of the body; the quantity of heat *dissipated* is measured by the calorimeter; and the quantity of heat *produced* is determined by the quantity dissipated plus any addition of heat to that of the body or minus any that is lost (p. 588). The *calorie*, or heat unit, is the quantity of heat that is necessary to raise the temperature of one gram of water 1° C.; the mechanical unit, or *grammeter*, is the quantity of energy required to raise one gram a height of one meter, and is equal to 424.5 calories; a *kilocalorie* or *kilogramdegree* is equal to 1000 calories, and a *kilogrammeter* to 1000 grammeters. By *specific heat* is meant the quantity of heat required to raise the temperature of any substance 1° C., this quantity varying considerably for different substances. If water be taken as 1, as a standard of comparison, the specific heat of the animal body may be regarded as being about 0.8; in other words, 0.8 of the quantity of heat will be required to heat the same weight of the animal body as to heat the water. Knowing the weight,

specific heat, and temperature of any substance the total quantity of heat stored in it at a given temperature may be readily calculated. Thus, if the animal experimented upon weigh 20 kilos, its specific heat be 0.8, and its temperature be 39°, the total quantity of heat stored would be $20 \times 0.8 \times 39° = 62.4$ kilogramdegrees. In calorimetric work the total heat in the organism is seldom considered, but the specific heat of the organism is of importance in determining the quantity of heat involved in a change of the animal's temperature. For instance, should the animal weigh 20 kilograms and its temperature be increased or decreased 0.2°, the quantity of heat added to or taken from the heat of the body, as the case may be, would be $20 \times 0.8 \times 0.2 = 3.20$ kilogramdegrees. These calculations are of fundamental importance in studying heat-production and heat-dissipation.

In making estimates of the dissipation of heat no regard is paid usually to the quantity lost in the urine and feces, because the error involved is so slight, but the quantities imparted to the air, both in warming the inspired air and in evaporating water from the lungs and skin, represent important percentages.

Calorimetry is spoken of as direct and indirect. The former method is the direct determination of the amount of heat produced and dissipated; the latter is the indirect determination based upon estimates of the quantities of O absorbed and CO_2 eliminated, or upon the amount of potential energy ingested in the food and probably transformed into kinetic energy within the body (p. 582).

Calorimeters of various forms have been employed, some of which have been devised to study the body as a whole, while others are adapted only for studying parts, such as a leg or arm. They may be classified as *ice, air,* and *water* calorimeters in accordance with the chief medium employed to absorb the heat. They consist essentially of an insulated jacket of ice, air, or water, which encloses the animal and serves to absorb the heat. The ice calorimeter is impracticable for physiological uses because the animal is placed under such abnormal temperature conditions; the air calorimeter has many inherent defects, and until very recent years has found but little acceptance; the water calorimeter is the form of apparatus usually employed, having been first used by Crawford in 1788; it has been materially modified by Despretz and Dulong and subsequent investigators. The now classical instrument of Dulong consists of two concentric cases. The animal is placed within the smaller case, which is submerged in the water contained in the larger case, this in turn being placed within a large box, between which and the calorimeter some non-conducting material such as feathers or wool is packed. Suitable openings are made for the proper supply of fresh air and for the agitation of the water in the calorimeter so that an equalization of the temperature of the instrument can be obtained. This apparatus has certain serious defects, however, which render it troublesome for expeditious and accurate work. An improved form devised by the author [1] which is now in general use meets every essential requirement for a satisfactory instrument. The apparatus con-

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[1] Reichert: *University Medical Magazine*, 1890, vol. 2, p. 173.

sists of two concentric boxes of sheet metal which are fastened together so that there is space of about one and a half inches between them filled with water (Fig. 142). The outer box is fifteen inches in height and width, and eighteen
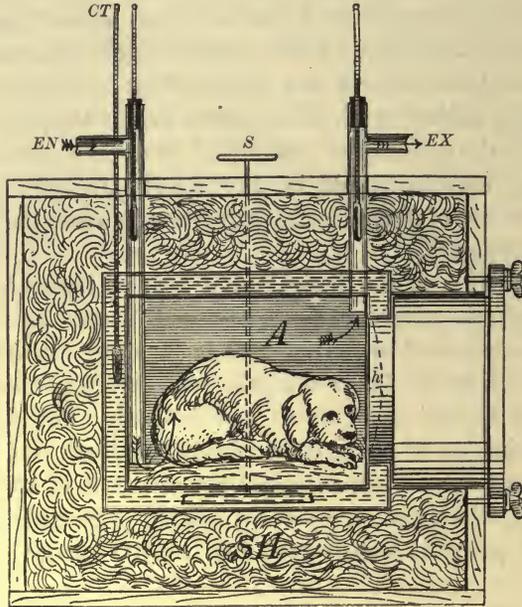
Fig. 142.—Reichert's water calorimeter.

inches in length. An opening (*h*) nine inches in diameter is made in one end for the entrance and exit of the animal. It is also perforated with three small holes in the top corners, and a slit-like opening in the top on one side. Two of the holes are for the tubes for the entrance and exit of air (*EN, EX*), the entrance tube being carried close to the bottom, while the exit tube extends only to the top of the box, and is placed in the opposite diagonal corner, thus ensuring adequate ventilation. In the third hole a thermometer (*C T*) is inserted, by means of which the temperature of the calorimeter (jacket of metal and water) is obtained. The opening in the side is for the insertion of a stirrer (*S*), which is for the purpose of thoroughly mixing the water and thus equalizing the temperature of both water and metal—in other words, of the calorimeter.

Before using the apparatus the *calorimetric equivalent* must be determined, that is, the amount of heat required to raise the temperature of the instrument 1°. This may be obtained indirectly by knowing the different substances used in the construction of the instrument, their weights, and their specific heats, and estimating from these data. It is better, however, to make the determination by burning a definite amount of absolute alcohol or hydrogen within the instrument, or by using a sealed vessel of hot water of a known temperature and allowing it to cool to a definite extent. The process is simple; for instance, each gram of alcohol or each liter of hydrogen completely oxidized yields a definite number of calories; similarly, a definite weight of water cooled a

definite number of degrees gives off a definite quantity of heat. The heat thus generated by the oxidation of the alcohol or hydrogen or given off by the cooling of the water is imparted to the calorimeter and increases its temperature. Knowing the quantity of heat given to the calorimeter and the increase of temperature of the instrument, the determination of the calorimetrical equivalent may be easily made. Thus, 1 gram of alcohol yields in round numbers 9000 calories; if we burn 10 grams of absolute alcohol, 90,000 calories will result; if the temperature of the calorimeter be increased 1°, the calorimetric equivalent will be 90,000 calories or 90-kilogramdegrees; in other words, for each degree of increase of the temperature of the calorimeter a quantity of heat equivalent to 90 kilogramdegrees is absorbed.

The heat dissipated by an animal is only in part absorbed by the calorimeter, another portion being given to the air which passes from the instrument, and another portion to water which is evaporated from the lungs and skin. Three estimates, therefore, are necessary—(1) of the heat given to the calorimeter, (2) of the heat given to the air, and (3) of the heat given off in the evaporation of water.

The estimate of the heat given to the air necessitates the measurement of the quantity of air supplied to the calorimeter, and of the temperature of the air on entering and leaving the calorimeter; while the estimate of the heat lost in evaporating water involves the measurement of samples of the air entering and leaving the instrument and of the quantities of water in both cases, the total quantity of water evaporated from the animal being estimated from these data.

The conduct of such experiments is not attended with any material difficulties. The water of the calorimeter is stirred for a sufficient length of time in order to obtain a uniform temperature. The temperature of the animal is taken and the animal then placed within the animal chamber. The temperatures of the calorimeter and of the air entering and leaving the instrument, and readings of the three gas-meters are recorded. During the progress of the experiment air temperatures are recorded at regular intervals of ten or fifteen minutes and the water stirred for a few seconds each time. At the conclusion of the experiment there are recorded—the temperature of the calorimeter, the temperatures of the air entering and leaving the calorimeter, the quantities of air passing through the three gas-meters, and the temperature of the animal.

The quantity of heat given to the *calorimeter* is now determined by multiplying the increase of temperature of the instrument by the calorimetric equivalent. If the rise of temperature be 0.6° C. and the calorimetric equivalent be 90 kilogramdegrees, the quantity of heat imparted to the water jacket will be 90 × 0.6° = 54 kilogramdegrees.

The quantity of heat imparted to the *air* is determined by finding first the corrected volume of the air, then reducing the corrected volume to weight, then multiplying the weight by the specific heat of air at 0° C., and finally multiplying by the increase of temperature. The corrected volume may be

obtained by the following formula: $V = \dfrac{V'\ P}{760\,(1 + 0.003665\,t)}$, where V is
the required volume at 0° C. and 760 mm. barometric pressure, V′ the ob-
served volume, P the observed pressure, and t the observed mean temperature:
760 (1 + 0.003665) is conveniently obtained from standard tables. The errors
incident to changes in barometric pressure and in aqueous tension are so slight
that they are not usually taken into consideration. Assuming that the quan-
tity of air supplied amounted to 6000 liters, and that the mean temperature
of the air was 20°, the corrected volume would be, omitting barometric
pressure and aqueous tension, $V = \dfrac{V'}{(1 + 0.0036656\,t)} = \dfrac{6000}{1,0733} = 5590$ liters
at 0° C. One litre of dry air at 0° C. weighs 0.001293 kilogram; therefore,
5590 liters × 0.001293 = 7.228 kilograms. If we assume that the air during
its passage through the calorimeter had its temperature increased 3°, and the
specific heat of air is 0.2377, the quantity of heat imparted to the air must
have been 7.228 × 3 × 0.2377 = 5.152 kilogramdegrees.

The next estimate is of the quantity of heat lost in the *evaporation of
water*. This is determined by finding the difference between the quantities
of water in the samples of the air passing into and from the calorimeter, and
estimating from these results the amount of moisture imparted to the total air
leaving the chamber. Assuming that 10 grams of water were thus evaporated,
since each gram requires about 582 calories or 0.582 kilogramdegree, the quan-
tity of heat evolved would be equal to 10 × 0.582 = 5.82 kilogramdegrees.

The total quantity of heat dissipated would therefore be the sum of the
quantities given to the calorimeter, to the air, and to the water evaporated:

Given to the calorimeter . . . . 54,000 kilogramdegrees.
Given to the air 5,152   "
Lost in evaporating water 5,820   "
    Total heat-dissipation 64,972   "

The *quantity of heat produced* is determined by adding to or subtracting
from the quantity dissipated the amount of heat that may have been gained
or lost by the organism. It is obvious that any difference between the
quantities of heat dissipated and produced must be represented by an increase
or decrease of the mean temperature of the animal. If the animal's tempera-
ture remains unchanged, the quantity of heat produced is the same as the
quantity lost; if, however, the animal's temperature increases, less heat is
dissipated than is produced; if it falls, *vice versa*. The quantity of heat
involved in a change of body-temperature is determined by the product of
the change in temperature into the animal's weight and specific heat. Assum-
ing that the animal's temperature at the beginning of the experiment was
38.95° C. and at the end 39.32° C., the temperature being increased 0.37° C.,
that the animal's weight was 25 kilograms, and that the animal's specific heat
was 0.8, the quantity of heat would be 0.37 × 25 × 0.8 = 7.4 kilogramdegrees.

The quantity of heat produced would, therefore, be the total quantity dissipated plus the quantity of heat added to the heat of the organism at the time the experiment begun; therefore, the heat-production was $64.972 + 7.4 = 72.372$ kilogramdegrees. If the animal's temperature had fallen, more heat would have been dissipated than produced, because the total quantity of heat in the organism was greater at the beginning than at the end of the experiment; therefore, the quantity of heat represented in the change of temperature would have been deducted from the quantity of heat dissipated.

While calorimetric experiments do not generally involve any special difficulties, accurate results can only be ensured by the strict observation of certain details: (1) The temperatures of the calorimeter and room should be as nearly as possible alike and kept as far as possible constant. (2) The thermometers employed should be so sensitive that readings can be made in hundredths of a degree, and they should respond very quickly, so that rectal temperatures can be obtained within three minutes. (3) Rectal temperatures are to be preferred, the thermometer always being inserted to the same extent and held in the same position, care being exercised to prevent the burying of the bulb in fecal matter. (4) The animal during the taking of its temperature must on no account be tied down, but gently held, and all circumstances seduously avoided that tend to excite the animal. The chief sources of error in the calorimetry are in failures to obtain accurate temperatures of the calorimeter and of the animal. In the latter case inaccuracy is to some extent absolutely unavoidable, chiefly because of normal fluctuations which occur frequently and are often very marked.

Conditions affecting Heat-production.—The quantity of heat produced must necessarily vary with many circumstances. Estimates of heat-production in the adult range in round numbers from 2000 to 3000 kilogramdegrees per diem according to the method and incidental circumstances. Thus, according to—

Scharling	3169 kilogramdegrees	Ranke	2272 kilogramdegrees
Vogel	2400 "	Rübner	2843 "
Hirn	3725 "	Ott	103 "
Leyden	2160 "	per hour during the afternoon (weight of
Hemholtz	2732 "	man 87.3 kilograms).
Rosenthal	2446 "	Lichatschew . . . . 33.072 to 38.723 kilo-
Danilesky	3210 "	gramdegrees per kilogram of body-weight
Ludwig	3192 "	per diem.[1]

The chief conditions which affect heat-production are age, sex, constitution, body-weight and body surface, species, respiratory activity, the condition of the circulation, internal and external temperature, food, digestion, time of day, muscular activity, the activity of heat-dissipation, nervous influences, drugs, abnormal and pathological conditions.

[1] The figures by Ott (*New York Medical Journal,* 1889, vol. 16, p. 29) and Lichatschew (*Diss. inauguralis,* St. Petersburg, 1893; quoted in Hermann's *Jahresberichte der Physiologie,* 1893, p. 99) were obtained by means of a water calorimeter.

Young animals produce more heat, weight for weight, than the mature. This is owing chiefly to the greater activity of the metabolic processes in the former, and in part to the relatively larger body surface, young animals generally being smaller than the matured and thus having, in proportion to body-weight, larger radiating surfaces.

Heat-production is more active in the robust than in the weak, other conditions being the same.

The weight of the body is obviously a most important factor in relation to the quantity of heat produced, especially as regards the weight of the active tissues in relation to inactive structures such as bone, sinew, and cartilage. Two animals of the same weight may produce very different quantities of heat per diem, other things being equal. Thus, a fleshy animal should naturally be expected to produce more heat than one with very little flesh and an abundance of fat, which is an inactive heat-producing structure. While, therefore, the relation of heat-production to body-weight does not seem to be definite, yet the experiments by Reichert[1] and by Carter[2] indicate that heat-production bears, broadly speaking, a direct relation to body-weight.

Heat-production is greater relatively in homothermous than in poikilothermous animals; it varies materially in intensity in different species, especially in warm-blooded animals; and it is closely related to the intensity of respiration. Moreover, it is probable that each species, and even each individual of the species, has its own specific thermogenic coefficient, that is, a mean standard of heat-production for each kilogram of body-weight or for each square centimeter of body-surface. The following figures giving the heat-production per kilogram per hour, compiled by Munk,[3] are of interest both as regards species and size and weight of the animal in relation to heat-production:

Horse	1.3 kilogramdegrees.	Duck	6.0 kilogramdegrees.
Man	1.5 "	Pigeon	10.1 "
Child (7 kilograms) . .	3.2 "	Rat	11.3 "
Dog (30 ") . .	1.7 "	Mouse	19.0 "
Dog (3 ") . .	3.8 "	Sparrow	35.5 "
Guinea-pig	7.5 "	Greenfinch	35.7 "

These figures have an additional interest when compared with the respiratory activity of different species (p. 537). The intensity of respiration has a marked significance both in connection with the species and the individual. The larger the quantity of oxygen consumed the greater relatively is the activity of oxidation processes, and, consequently, the more active is heat-production (see p. 537). Therefore, all circumstances which affect respiratory activity tend to affect thermogenesis. The intensity of respiratory activity and the extent of body-surface in relation to body-weight are closely related (p. 538).

Increased activity of the circulation is favorable to increased heat-produc-

[1] *University Medical Magazine*, 1890, vol. 2, p. 225.

[2] *Journal of Nervous and Mental Diseases*, 1890, vol. 17, p. 782.

[3] *Physiologie des Menschen und der Saugethiere*, 1892, p. 302.

tion, this being due to several factors: (1) A more abundant supply of blood may be accompanied by increased metabolic activity. (2) Increased circulatory activity is favorable to increased heat-dissipation by causing a larger supply of blood to the skin, thus facilitating loss by radiation and indirectly tending to increase thermogenesis. (3) Increased circulatory activity also excites the respiratory movements and the secretion of sweat, thus increasing heat-loss and indirectly favoring heat-production. (4) The more active the circulation the larger the amount of heat produced by the heart and the movement of the blood. The diurnal fluctuations of the pulse-rate are said to be more or less closely related to similar changes of body temperature.

A rise of internal temperature (bodily temperature) is favorable to increased metabolic activity (p. 540) and, therefore, to an increase of heat-production; conversely, a fall of bodily temperature reduces heat-production. The influences of bodily temperature are, as a whole, less important than those of external temperature.

The influences of external temperature are in a measure different upon homothermous and poikilothermous animals. In the former, heat-production is in inverse relation to the temperature of the surrounding medium, so that the cooler the ambient temperature the greater the heat-production; in the latter heat-production increases with an increase of external temperature, because with the rise of the latter bodily temperature increases, which in turn increases metabolic activity (pp. 540, 541). Consequently, in warm-blooded animals heat-production is greater in cold climates and seasons than in the opposite conditions, while in cold-blooded animals the opposite is the case. Cold applied to the skin increases heat-production by reflexly exciting muscular activity (shivering, etc., p. 541); moderate heat exerts the opposite influence unless the bodily temperature is affected, as shown by the results of studies of respiration (p. 541).

The character of the food is important. Danilewsky[1] has estimated that the following quantities of heat are produced under different diets, etc.:

On a minimum diet . . . . 1800 kilogramdegrees.
On a reduced diet (absolute rest) 1989   "
On a non-nitrogenous diet 2480   "
On a mixed diet (moderate work) 3210   "
On an abundant diet (hard work) 3646   "
On an abundant diet (very laborious work) 3780   "

The influence of the quantity and quality of the diet must be potent when it is remembered that 1 gram of proteid yields about 4937 calories, 1 gram of fat about 9312 calories, and 1 gram of carbohydrate about 4116 calories. In cold climates fats enter very largely into the diet because of the greater loss of heat and the consequent increased demand for heat-producing substances.

During the periods of digestion more heat is produced than during the intervals, this increase being due chiefly to the muscular activity of the intestinal walls (p. 540). Langlois' experiments indicate that during digestion heat-production may be increased 35 to 40 per cent.

[1] *Pflüger's Archiv für Physiologie*, 1883, vol. xxx. p. 190.

It is said that heat-production undergoes diurnal variations which correspond with the fluctuations of bodily temperature, but this is doubtful.

All structures produce more heat during activity than during rest. Heat-production has been estimated to be from two and a half to three times greater when awake and resting than when asleep, and from one and a half to three times more when active than when at rest, in proportion to the degree of activity. During hybernation the absorption of O falls considerably (p. 542), consequently heat-production is believed to decline to a like degree.

All circumstances which affect heat-dissipation (p. 601) tend indirectly to influence heat-production.

The most important of the factors influencing heat-production is the nervous mechanism which controls the heat-producing processes (p. 598).

Various drugs exert more or less potent influences directly or indirectly upon heat-production. Cocain, strychnin, brucin, and other motor excitants increase heat-production; while chloroform, most antipyretics, narcotics generally, bromides, and motor depressants decrease heat-production.

Heat-production is diminished in most forms of anæmia, after severe hemorrhage, and in most non-febrile adynamic conditions. It is usually increased in fevers, especially so in infectious fevers. According to Liebermeister, the increase in fever is probably about 6 per cent. for each increase of 1° C. of bodily temperature, so that were the increase of temperature 3° C. the increase of heat-production would be 18 per cent.

Conditions affecting Heat-dissipation.—The loss of heat from the body occurs through several channels—in the urine, feces, sweat, and expired air, and by radiation and conduction from the skin; hence, all conditions which affect the loss of heat in the above ways must influence heat-dissipation. The chief of these are: Age, sex, species, the quantity of subcutaneous fat, the nature of the surrounding medium, clothing, internal and external temperature, activity of heat-production, body-surface, the condition of the circulation, respiration, sweat, activity, radiating coefficient, nervous influences, drugs, and abnormal conditions.

The young dissipate and produce more heat in proportion to body-weight than the adult, this being due chiefly to the relatively greater metabolic activity and the larger proportional body-surface (p. 538), and consequent greater radiation, in the young.

Sex *per se* does not seem to exert any influence, although the adult human female, weight for weight and for an equivalent bodily surface, probably dissipates less heat than the male, because of her relative abundance of subcutaneous fat, which hinders heat-dissipation. No difference so far as sex is concerned has been noted in the lower animals.

Heat-dissipation varies greatly in different species, owing chiefly to relative size and respiratory activity, to the nature of the medium in which the animal lives, and to the character of the body-covering. Heat-dissipation is more active in homothermous animals than in poikilothermous animals, because of the greater activity in the former of heat-production. In amphibia heat-dissi-

pation is greater when the animal is in the water than when exposed to the air if both water and air be of the same temperature, because water is a better conductor of heat and consequently withdraws heat from the body more rapidly. The higher the temperature of the surroundings the higher the bodily temperature of cold-blooded animals, consequently the greater are heat-production and heat-dissipation. In warm-blooded animals the effect on both heat-production and heat-dissipation is in inverse relation to the surrounding temperature (unless the bodily temperature is affected), external heat decreasing both heat-dissipation and heat-production, and internal heat increasing both.

Subcutaneous fat is a poor conductor of heat, consequently the greater the abundance of it the greater the hindrance offered to the dissipation of heat. The value of fat in this respect is illustrated in water-fowl, which, as a rule, are far more abundantly supplied with fat than other species; and by the exceptional abundance of subcutaneous fat in species of fowl which inhabit very cold waters. Bathing the skin with grease hinders radiation, and is adopted by swimmers both to conserve the bodily heat and to protect the skin.

When air and water are of the same temperature, heat-dissipation is greater when the animal is exposed to the water, because the latter is a better conductor. Heat-loss is greater in dry than in moist air, other things being equal, because in the former the evaporation of sweat from the body and the loss of water from the lungs are favored, the vaporization of water affecting heat-dissipation more decidedly than the moisture of the air. Heat-dissipation is more active in cold moist air than in cold dry air. Cold air is not favorable to the vaporization of water, whereas cold moist air has a higher specific heat than the dry air, and thus tends to carry off heat more rapidly.

The character of the covering of the body is of great importance. This is illustrated in the changes which occur in the natural covering of animals during warm and cold seasons, and in the characters of the fur of species which inhabit very cold or very warm climates. During the winter the fur is longer and thicker than during the summer. Animals living in cold or hot climates are supplied with a relatively greater or less abundance of fur or feathers and subcutaneous fat. Man provides for changes of the seasons by modifying the quantity and quality of his clothing. In the adaptation of dress to climate, the conductivity, radiating coefficient, hygroscopic capacity, porosity, weight, and color of the clothing are important factors. The poorest conductors, other things being equal, make the warmest clothing; fur and wool are poor conductors and therefore are adapted especially for cold seasons and climates, while cotton and linen are good conductors and therefore make cool clothing. The radiating coefficient depends upon the conductivity of the material and the character of the radiating surface. The coarser the material the better the radiating surface, hence the better the conductor and the cooler the clothing. The hygroscopic character of the clothing is of far more importance than is generally believed. Articles of clothing having a large capacity for absorbing and retaining moisture are, other things being equal, of more value, especially for underwear, than those possessing the opposite

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quality. Woollen goods compared with those made of cotton not only have a far greater absorptive capacity but retain moisture for a longer time. When the clothing is of wool people are less apt to catch cold from exposure to draughts and sudden cold than when it is of linen or cotton, the wool preventing a too rapid evaporation of moisture, thus guarding against chilling. Porosity is a comparatively subsidiary factor. The greater the weight of the clothing, other things being equal, the more is heat-dissipation hindered. The color of the outer apparel has a certain influence owing to the relative heat-absorbing capacities, black clothing being warmer than white, etc., hence the general use of white or light-colored clothing in warm climates and seasons.

A rise of internal temperature (bodily temperature) is favorable to an increase of heat-dissipation, for several reasons : (1) Heat-production tends to be increased and thus cause an effort of the system to get rid of the excess of heat. (2) The activity of the circulation is increased, causing a larger amount of blood to be brought to the cutaneous surface where it is subjected to the influence of the cooler surroundings. (3) Respiratory movements are increased so that heat-dissipation is favored by the larger amount of air respired and larger amount of moisture carried off. (4) The temperature of the body is higher in relation to that of the surroundings and thus heat-dissipation by radiation and conduction is facilitated. The influences of external temperature are even more potent in their effects than those of internal temperature, chiefly because of the much wider range of temperature to which the organism is subjected. Bodily temperature under ordinary circumstances does not vary more than $1°$ to $2°$ C. during the twenty-four hours, but external temperature may vary as much as $40°$ C., or more. External heat tends by exciting cutaneous nerves to reflexly diminish heat-production and thus indirectly diminish heat-dissipation ; but this is to some extent antagonized by a dilatation of the blood-vessels of the skin, an excitation of respiration, and increase in the quantity of sweat, all of which tend to increase heat-dissipation, but which are unable to balance the opposite effects. Cold, on the other hand, accelerates both heat-dissipation and heat-production. The loss of heat from the body is increased because of the greater difference in the temperatures of the body and the surroundings ; but, on the other hand, the cutaneous vessels are contracted, the circulation is less active, and the quantity of sweat is lessened, all of which are unfavorable to heat-dissipation. Yet while these latter alterations tend to diminish heat-loss, they are not sufficient to compensate for the increased expenditure by radiation and for the greater loss by respiration.

Circumstances which increase heat-production above the normal tend indirectly to increase heat-dissipation. Other things being equal, the greater the quantity of heat produced the greater the heat-dissipation, unless the bodily temperature be below the normal, in which case heat-production may be increased and yet heat-dissipation remain unaffected, or even be diminished, until sufficient heat has accumulated to bring the bodily temperature up to the mean standard.

The larger the surface of the body exposed to the normally cooler sur-

roundings, the greater is the loss of heat. The larger the animal the greater the body-surface, and therefore the greater is heat-dissipation; but in proportion to body-weight smaller animals have larger body-surfaces, therefore heat-dissipation is *relatively* greater, although not absolutely so (see p. 537). The area of body-surface involved in heat-dissipation is affected by the position of the individual. Thus, by bringing the arms and legs in contact with the body the total surface exposed is lessened. On the other hand, animals which habitually have their legs in apposition with the trunk have their radiating surfaces increased when their legs are extended. For instance, in the rabbit extension of the legs enormously increases heat-dissipation, so that the bodily temperature is profoundly affected.

The condition of the vascular system exercises an important influence. Circumstances that excite the circulation affect heat-dissipation both directly and indirectly. Thus, heat-loss is directly increased by the excitation of the respiratory movements, by the increased secretion of sweat, and by the larger supply and increased temperature of the blood to the skin. Increased activity of the circulation also increases heat-production, and thus indirectly affects heat-dissipation. Opposite conditions, of course, lessen heat-dissipation.

The larger the quantity of air respired, other things being equal, the larger the loss of heat by this channel. The heat-loss occurs both in warming the air and in the evaporation of water from the lungs, so that the cooler and drier the air inspired the larger relatively is the heat-loss. The importance of respiration as a heat-dissipating factor is illustrated by the fact that about 10.7 per cent. of the total heat-dissipation occurs in this way (see p. 584).

Next in importance to radiation is the amount of water evaporated from the skin. Each gram of water requires 582 calories to vaporize it, and it is estimated (p. 584) that 364,120 calories are dissipated in this way, or 14.5 per cent. of the total heat-dissipation. An increase of external temperature increases the irritability of the sudoriparous glands, thus favoring secretion and heat-dissipation. The value of sweat, however, as a means of carrying off heat, is materially affected by the temperature of the air as well as by the amount of moisture present. The higher the temperature and the less the moisture the more rapidly evaporation occurs, and consequently the greater the loss of heat; when air is moist and of high temperature evaporation takes place relatively slowly, if at all. Therefore, individuals can withstand subjection to dry air of a higher temperature and for a longer period than when the atmosphere is moist. In the former case sweat is rapidly secreted and vaporized, and thus a marked rise of internal temperature may be prevented. James found that a vapor bath at 44.5° C. (112° F.) was insufferable, while dry air at 80° C. (176° F.) caused little inconvenience. When air is of high temperature and loaded with moisture we say that it is "sultry," but dry air of the same temperature is not unpleasant.

Muscular activity increases heat-production, excites the circulation and respiration, and increases the secretion of sweat, all of which directly or indirectly increase heat-dissipation.

The surface of the body as a radiating surface cannot be regarded in the same light as an indifferent, inanimate surface, such as metal or wood. The *coefficient of radiation* (the quantity of heat emitted during a unit of time at a standard temperature from a given area) in an inanimate body remains fixed, because the surface itself is virtually unchangeable; but the coefficient for the living organism is subject to material alterations. These alterations depend chiefly (1) upon the actions of the pilo-motor mechanism whereby the relation of the natural covering (hair or feathers in the lower animals) of the body to the skin is effected; (2) upon changes in the conductivity of the skin owing to variations of the blood-supply; (3) upon the varying thickness of the skin in different species, in different individuals, and in different parts of the body; (4) upon the temperature of the surroundings; (5) upon the extent of the body-surface exposed; (6) upon the character of the clothing. When the arrector pili muscles contract the skin is made tense and the cutaneous blood-vessels are pressed upon and rendered anæmic, thus lessening the quantity of fluid in the skin and as a consequence lowering the coefficient of dissipation; moreover, in animals whose natural covering is fur or feathers, these fibres cause an erection of one or the other, as the case may be, and in this way affect the radiating coefficient. The coefficient is enormously increased by removing the natural covering, such as the fur of the rabbit, under which circumstances, even though the animal be subjected to a relatively high external temperature, heat-dissipation is so enormously increased that death ensues within two or three days. When one side of the body of a horse was shaved and the animal subjected to an atmosphere having a temperature of 0° C., the temperature of the skin of the shaven side fell 8° in forty minutes, while the temperature of the unshaven side fell only 0.5°.

The coefficient is diminished where there is excessive sebaceous secretion, and where grease is artificially applied, and by an accumulation of subcutaneous fat; it is increased by wetting the skin, as by sweat or bathing; and it is affected by many other circumstances.

Through the operations of the nervous system heat-dissipation may be affected directly or indirectly by action upon the heat-dissipating and heat-producing processes—circulation, respiration, sudorific and sebaceous glands, and arrector pili muscles.

There are many drugs which directly or indirectly affect heat-dissipation. Drugs which cause dilatation of the cutaneous vessels tend to increase heat-dissipation; conversely, those which cause contraction of the blood-vessels hinder dissipation. Diaphoretics increase heat-loss essentially by increasing the amount of sweat. Respiratory excitants increase the loss of heat by means of the increased volume of air respired. Drugs which increase heat-production tend to indirectly increase heat-dissipation.

All pathological states which affect heat-production tend to similarly disturb heat-dissipation. Conditions of malnutrition favor heat-dissipation by causing a loss of subcutaneous fat, but this is to a greater or less extent compensated or by the enfeeblement of the circulation, respiration, and metabolic processes

in general. In fever, both heat-production and heat-dissipation are generally increased, the former being affected more than the latter, so that the bodily temperature rises. In some forms of fever the rise of temperature is essentially due to diminished heat-dissipation.

D. THE HEAT-MECHANISM.

The heat-mechanism consists of two fundamental parts, one being concerned in heat-production, and the other in heat-dissipation. Heat-production is briefly expressed as *thermogenesis;* and heat-dissipation, as *thermolysis.* The operations of these mechanisms are so intimately related that fluctuations in the activity of one are rapidly compensated for by reciprocal changes in the other, so that under normal conditions heat-production and heat-dissipation so nearly balance that the mean bodily temperature is maintained within narrow limits.

The regulation of the relations between heat-production and heat-dissipation is termed *thermotaxis*, which regulation may be effected by alterations in either thermogenesis or thermolysis.

The Mechanism concerned in Thermogenesis.—The portion of the heat-mechanism concerned in heat-production consists of (1) thermogenic tissues, (2) thermogenic nerves, and (3) thermogenic centres.

The Thermogenic Tissues.—Almost if not every tissue of the body may be regarded as being a heat-producing structure. The very fact that oxidative processes lie at the bottom of all forms of vital activity, and that heat-production is a concomitant of oxidation, leads inevitably to the conclusion that as long as cells possess life they must produce heat. There are, however, certain of the bodily structures, especially the skeletal muscles and the glands, which are exceptionally active as heat-producers. Indeed, in the case of the skeletal muscles the heat-producing processes are of such a character as to justify the belief that with them thermogenesis is a specific function, because heat is produced not merely as an incidental product of activity but as a specific product. When a muscle contracts, heat is evolved as an incident of the performance of work, and when it is at rest heat is produced not only as an incident of growth and repair but as the result of a specific act. This latter is proved by the fact that when the muscles have been in a state of prolonged rest, when the chemical changes concerned in growth and in repair of waste are inactive, heat-production continues to a marked degree. Moreover, the quantity which is produced varies with the immediate needs of the economy and bears a reciprocal relationship to the quantity of heat formed in other structures,[1] and is regulated apparently by specific nerve-centres.

When the muscles are contracting less than one-fifth of the energy appears as work, and more than four-fifths as heat. The contractions of the heart also furnish an appreciable percentage of heat as an accompaniment of contraction; and considerable heat is formed indirectly by the resistance offered by the the blood-vessel walls to the blood current. Indeed, the entire work of the heart becomes converted into heat, representing from 5 to 10 per cent. of the

[1] Rübner: *Sitzungsberichte d. königl. Bayer. Akad. der Wissenschaft,* 1885, Heft 4.

total heat-production.   The quantity formed as by-products of the activity of various structures during a state of muscular quiet is doubtless small compared with the quantity produced by the muscles.

The Thermogenic Nerves and Centres.—Heat-production may occur independently of, but under normal circumstances it is regulated by, the nervous system. A muscle separated from all nervous influences continues to produce heat, but considerably less than before, and it ceases to respond to the demands of the system for more or less heat as do muscles with their nerves intact.   Injuries to certain parts of the cerebro-spinal axis affect heat-production in muscles, in some instances causing an increase and in others a decrease; but these changes do not occur if the nervous communication between the centres and muscles is destroyed.

Thermogenic Nerves.—Specific thermogenic nerve-fibres have not as yet been isolated, although the researches by Kemp [1] and Reichert [2] indicate that such fibres exist.   In muscles probably two kinds of katabolic processes go on, one subservient to muscular contraction and the other to heat-production.   From the fact that there may be two kinds of katabolic processes we are led to the conclusion that two corresponding sets of nerve-fibres control them, and it seems probable that the katabolic processes which give rise to muscular contraction and its accompanying heat-production are due to impulses carried to the muscles by motor nerves, while those specifically concerned in the production of heat are transmitted by nerve-fibres of an entirely different character, possibly those fibres subserving muscular tone.   Upon this hypothesis the latter fibres might be designated as specific thermogenic fibres— in other words, they are specifically engaged in conveying impulses from the nerve-centres to the muscles, bringing about katabolic changes which have for their especial object the production of heat.   According to another hypothesis both muscular contraction and muscular tone are subserved by the motor nerves, whether or not contraction results being a question of intensity of the impulses.

Our knowledge of the character of the afferent fibres which carry impulses that reflexly affect thermogenesis is very unsatisfactory.   There can be no doubt that sensory impulses arise in various parts of the organism, especially in the skin, which exercise important influences upon the heat-producing processes.   Thus, cooling the skin reflexly excites heat-production, which cannot be attributed to indirect influences upon other functions, but whether or not there exist specific afferent thermogenic fibres is not known.   It is possible that the temperature nerves of the skin, the cold and the heat nerves, may be responsible for reflex excitation or depression of heat-production.

The Thermogenic Centres.—The existence of specific thermogenic centres has for many years been conceded, but it has only been recently that hypothesis has given place to fact.   The most important results of recent research may be generalized as follows: (1) That the irritation of the skin by heat or cold is followed by marked changes in thermogenesis, which effects are to a certain extent entirely independent of vasomotor and other incidental changes, and which, therefore, are due in part to an increase of heat-production dependent

[1] *Therapeutic Gazette*, 1889, p. 155.   [2] *Ibid.*, 1891, p. 151.

directly upon efferent thermogenic impulses. (2) That injury or excitation of certain parts of the brain is followed by an increase of heat-production. (3) That injury or excitation of certain other parts of the brain is followed by diminished heat-production. (4) That injury of the spinal cord may be followed by an increase or decrease of heat-production which cannot be entirely accounted for by vaso-motor and other attendant alterations. (5) That after operations upon certain parts of the cerebro-spinal axis there follows an increase or decrease in the quantity of CO_2 formed, indicating a corresponding effect on the heat-producing processes.

The results of recent calorimetric work show that there are definite regions of the cerebro-spinal axis which are apparently specifically concerned in thermogenesis; that the effects of excitation or destruction of each region are more or less characteristic; and that the different regions seem to be so intimately related to one another as to constitute a co-ordinate mechanism. Certain of these regions when irritated give rise, as a direct result, to increased thermogenesis, hence they are of the nature of *thermo-accelerator* centres; and others to diminished thermogenesis, hence are *thermo-inhibitory* centres. Both kinds of centres seem to be associated with and to govern a third kind which is distinguished as the *general* or *automatic* thermogenic centres. The mechanism may be theoretically expressed in this form: The general thermogenic centres may be regarded as maintaining by virtue of independent activity a fairly constant standard of thermogenesis, and as being influenced to increased activity by the thermo-accelerator centres and to diminished activity by the thermo-inhibitory centres. The finer or smaller variations in thermogenesis are presumably effected by the general centres, whereas the grosser variations are probably effected by the influences of the thermo-accelerator and thermo-inhibitory centres.

Specific heat-centres (thermogenic and thermolytic) have by various observers been held to exist in certain regions of the brain cortex, in the base of the brain just in front of and beneath the corpus striatum, in the corpus striatum, in the septum lucidum and the tuber cinereum, in the optic thalamus, in the corpora quadrigemina, in the pons and medulla oblongata, and in the spinal cord. Some of these centres have been regarded as being thermogenic and others as being thermolytic. Many errors in deduction have, however, been made because of the many inherent difficulties attending experimentation upon the cerebro-spinal axis, and because almost all the methods used necessarily involve injury or excitation of contiguous parts. The methods adopted of studying these various regions have been chiefly destruction or injury by means of a probe, actual cautery, excision, and the injection of cauterants; by transverse incisions across the cerebro-spinal axis so as to separate higher from lower portions of the cerebro-spinal axis; and by excitation by small punctures, electricity, etc.

In classifying these centres we are governed by the results which follow excitation and destruction. When irritation or destruction directly affects thermogenesis, the centre is regarded as being thermogenic, but if heat-dissipation is the process directly affected, the centre is regarded as being thermo-

lytic. In classifying thermogenic centres we would regard the centre as being a general thermogenic centre if it is capable, after the destruction of other thermogenic centres, of causing the normal output of heat; a thermo-accelerator centre is distinguished by the fact that excitation increases thermogenesis, while destruction does not diminish thermogenesis, unless the centre happens to be active at the time, and further by the fact that after its destruction the normal output of heat may continue; a thermo-inhibitory centre is distinguished by a decrease of heat-production following stimulation and by the absence of any permanent effect on thermogenesis when the centre is destroyed. The general or reflex thermogenic centres are undoubtedly continuously active, the degree of activity varying according to the immediate demands of the organism for heat; while the thermo-accelerator and thermo-inhibitory centres are probably only intermittently active, coming into play when the general centres are of themselves unable to effect a sufficiently rapid compensation.

While it must be admitted that our knowledge of the precise locations, physiological peculiarities, and correlations of the thermogenic centres is by no means complete, we have at our disposal some most important and significant data. The general thermogenic centres have been shown by Reichert [1] to be located in the spinal cord. The thermogenic centres in the brain are either thermo-accelerator or thermo-inhibitory. Thermo-accelerator centres probably exist in the caudate nuclei (possibly also in the tuber cinereum and optic thalami), pons, and medulla oblongata. [2]

Excitation of any one of these regions is followed by a pronounced rise of heat-production; destruction of any one region may or may not be followed by a decrease of heat-production, and if a decrease does occur it may in most cases be attributed to incidental causes, such as shock and other attendant conditions. The centre which is common to the pons and medulla is for the most part probably located in the latter, but it is not so powerful in its influences on thermogenesis as the thermo-accelerator centres in the basal regions of the cerebrum. These cerebral centres are affected by agents which have little or no effect on the heat centres of the spinal cord. Thermo-inhibitory centres have been located in the dog in the region of the sulcus cruciatus and at the junction of the supra-Sylvian and post-Sylvian fissures. [3] Irritation of either of them is followed by a decrease of heat-production, while their destruction may be followed by a transient increase of heat-production. The cruciate centre is the more powerful. None of these cerebral centres exercises

[1] *University Medical Magazine*, 1894, vol. v. p. 406.

[2] Reichert: *University Medical Magazine*, 1894, vol. 6, p. 303. Ott: *Journal of Nervous and Mental Diseases*, 1884, vol. 11, p. 141; 1887, vol. 14, p. 154; 1888, vol. 15, p. 85; *Therapeutic Gazette*, 1887, p. 592; *Fever, Thermotaxia, and Calorimetry*, 1889. Aronsohn and Sachs: *Pflüger's Archiv für Physiologie*, 1885, vol. 37, p. 232. Girard: *Archiv de Physiologie normale et pathologique*, 1886, vol. 8, p. 281. Baginsky und Lehmann: *Virchow's Archiv für Pathologie*, 1886, Bd. 106, p. 258. White: *Journal of Physiology*, 1890, vol. 11, p. 1; 1891, vol. 12, p. 233. Baculo: *Centri temici*, 1890, 1891, and 1892. Tangl: *Pflüger's Archiv für Physiologie*, 1895, vol. 68, p. 559.

[3] Wood: "Fever," *Smithsonian Contributions to Knowledge*, 1880, No. 357. Ott: *Journal of Nervous and Mental Diseases*, 1888.

any influence on thermogenesis after section of the spinal cord at its junction with the medulla oblongata.

Theoretically, these centres are associated in this way : The general thermogenic centres are in the spinal cord, and while they are perhaps impressionable to impulses coming to them through various sensory nerves, they are not apparently in the least influenced by cutaneous impulses caused by changes in external temperature nor by changes of the temperature of the blood. It is not improbable that these centres are in the anterior cornua of the spinal cord. The thermo-accelerator and thermo-inhibitory centres are connected with the general centres by nerve-fibres, the former influencing the general centres to increased activity, and the latter to diminished activity. The thermo-accelerator and thermo-inhibitory centres seem to be especially affected by cutaneous impulses which are generated by changes in external temperature, and to be influenced by alterations of the temperature of the blood. It is doubtless through these centres that changes in external and internal temperature are able to affect the heat-producing processes. Presumably both an increase of temperature of the blood and cutaneous impulses generated by an increase of external temperature excite the thermo-inhibitory centres, and thus inhibitory impulses are sent to the general centres, lessening their activity ; on the other hand, both a fall of temperature of the blood and cutaneous impulses generated by cold presumably excite the thermo-accelerator centres and thus cause impulses to be sent to the general centres, exciting them to greater activity.

The Mechanism concerned in Thermolysis.—The loss of heat by the body is in a large measure incidental to attendant conditions and is not a reflex result of the activity of a thermolytic mechanism; in other words, the loss occurs essentially by virtue of the same conditions as would cause inanimate bodies to lose heat. The living homothermous organism differs as regards the loss of heat from dead matter, chiefly in that the rapidity with which heat-dissipation occurs is regulated to a material extent by vital processes. The regulation of the loss of heat is effected by the operations of a complex mechanism—that is, one consisting of a number of distinct although correlated parts. A study of this mechanism, which is designated the thermolytic mechanism, includes a consideration of all of the processes by which heat is lost, of the nervous mechanisms which govern them, and of the conditions which affect them, but especially of those processes and mechanisms which act reciprocally in conjunction with the thermogenic mechanism to maintain the mean bodily temperature. Practically all of the heat lost by the organism occurs by radiation and conduction from the skin, by the evaporation of water from the skin and lungs, and in warming the food, drink, and inspired air. From these facts we believe that mechanisms which affect the blood-supply to the skin, the quantity of sweat secreted, the condition of the surface of the skin, and the quantity of air inspired must in a large measure regulate thermolysis. For instance, if the temperature of the organism be materially increased there occur increased activity of the heart, peripheral vascular dilatation, increased respiratory activity, and (except in fever) an increase in the secretion of sweat. The increase of the

activity of the heart together with the dilatation of the cutaneous blood-vessels increases the quantity of blood supplied to the skin ; the cutaneous blood-vessels are dilated, exposing a larger surface of blood to the cooler external surroundings, and thus materially favoring the loss of heat by radiation ; the increase in the quantity of sweat is favorable to an increase in the amount of water evaporated, and thus to a larger loss of heat in this way ; an increase of respiratory activity means a larger volume of air respired, a greater expenditure of heat in warming the air and in the evaporation of water from the lungs. In man the pilo-motor mechanism plays a subsidiary and unimportant part in the regulation of heat-dissipation, but in some lower animals, as in certain birds, it is of considerable importance. The thermolytic mechanism therefore includes the cardiac, vaso-motor, respiratory, sweat, and pilo-motor mechanisms. All these are affected directly or indirectly by the temperature of the blood and skin. An increase in the temperature of the blood and skin excites all of them so that changes are brought about which favor heat-loss. The respiratory movements especially may be rendered intensely active, and in certain animals to such a marked degree that they may become more frequent than the heart-beats.

Thermotaxis.—Thermotaxis or heat-regulation is effected by reciprocal changes in heat-production and heat-dissipation brought about by the intervention of the thermogenic and thermolytic centres, just as the regulation of arterial pressure is effected by the reciprocal relations of the cardio-inhibitory and vaso-motor mechanisms. If heat-production is more active than heat-dissipation, thermolysis is so affected that the heat-loss is increased, and thus the mean bodily temperature maintained ; if heat-production is subnormal, heat-dissipation also falls. Similarly, if heat-dissipation is increased, the heat-producing processes are excited to greater activity to make up the loss ; conversely, if heat-dissipation is decreased, heat-production also tends to be decreased. These reciprocal actions depend essentially or wholly upon the influence of cutaneous impulses and the temperature of the blood. For instance, an increase of the temperature of the blood increases the activity of the thermolytic processes, thus effecting a compensation. If we subject an animal to a moderately cold atmosphere, as in the winter, heat-dissipation is increased, but cutaneous impulses are generated which excite the thermogenic centres so that heat-production is also increased, and thus the bodily temperature is maintained practically unaffected. It is only under abnormal conditions or under conditions of intense muscular activity that this reciprocal relationship is so disturbed that changes in one process are not quickly compensated for by changes in the other.

Thermotaxis is effected in a large measure reflexly, especially by cutaneous impulses generated by external cold and heat, both thermogenic and thermolytic processes being affected. Cold applied temporarily, as in the form of a douche, bath, sponging, etc., causes constriction of the cutaneous capillaries. This lessens both the quantity and temperature of the blood passing through the skin, the effect of which tends to decrease the dissipation of heat by radiation and conduction. Moreover, a lessened blood-supply causes the skin to

become poorer in fluid, so that the conduction of heat from the warmer inner parts is lessened. The conductivity of the skin is further decreased by the action of the pilo-motor muscles, which when in contraction or in a state of greater tonicity render the skin tenser and thus press out the blood and tissue juices. The secretion of sweat is diminished, so that the quantity of heat lost in the vaporization of water is decreased. On the other hand, heat-dissipation tends to be materially increased by the greater radiation of heat due to the greater difference between the temperature of the body and of the douche, bath, etc., and the tendency to an increase in this way is much greater than the opposite tendency depending upon the factors above noted, therefore heat-dissipation is increased. Bathing the skin with cold water increases heat-loss by the vaporization of water as well as by conduction.

The excitation of the cutaneous nerves by cold reflexly increases thermogenesis, and to such an extent that heat-production may even exceed the quantity dissipated, thus causing an increase of bodily temperature. This rise, which is transient, may amount to 0.2° C. or more, and is followed by a reaction in which the temperature may fall 0.2° C. or more below the normal, and continue subnormal for some hours; this fall in turn is succeeded by a supplementary reaction in which the temperature may rise slightly above the normal.

The chief reactions brought about by moderate external cold are constriction of the cutaneous blood-vessels, a diminution of the quantity of sweat secreted, increased tonicity of the pilo-motor muscles, and increased tonicity of the skeletal muscles. The action upon the latter muscles may be so marked as to cause shivering, which increases respiratory activity (see p. 540) and presumably similarly increases heat-production.

Moderate external heat causes dilatation of the cutaneous vessels, excites the general circulation and thus increases the blood-supply to the skin, excites respiratory movements and the sweat-glands, but decreases thermogenesis. Owing to the dilatation of the blood-vessels of the skin and the excitation of the circulation the temperature and the quantity of the blood supplied to the skin are increased, so that conditions are caused which are favorable to an increased loss of heat by radiation. Increased activity of the respiratory movements means a larger volume of air respired, and consequently a greater loss of heat in warming the air and in the evaporation of the larger quantity of water from the lungs. The increase in the quantity of sweat formed also favors heat-dissipation by means of the larger amount of water evaporated from the skin. When, however, the external temperature is higher than that of the body, loss of heat by radiation and conduction cannot occur, so that heat not only accumulates as a result of the interference with heat-dissipation, but by absorption.

The chief reactions brought about by moderate external heat are a dilatation of the cutaneous blood-vessels, excitement of the general circulation, an increase in the number of respiratory movements, increase in the amount of sweat, diminished tonicity of the muscles, and diminished thermogenesis which is probably due to a lessening of the activity of the chemical changes in the muscles.

When external temperature is excessive and continued, heat-regulation is rendered impossible : if extreme cold, heat-dissipation takes place more rapidly than heat-production, so that bodily temperature falls until death results ; if very hot, heat-dissipation is so interfered with that heat rapidly accumulates within the organism, causing a continuous rise of temperature which finally causes death.

Abnormal Thermotaxis.—By this term is meant the regulation of the heat-processes under conditions in which the mean bodily temperature is maintained at a standard above or below the normal, as in fever and in animals from which the hair has been shaved. It is assumed that under normal conditions the heat-centres are "set," as it were, for a given temperature of the blood, and that when the temperature of the blood goes above or below this standard a compensatory reaction occurs, so that thermogenesis and thermolysis are properly affected to bring about an adjustment. In fever it may be considered that the centres are set for a higher temperature than the normal ; the higher the fever, the higher the adjustment. The centres may be set for subnormal temperatures, as in the case of a rabbit shaved, whose temperature may remain 2° or 3° below the normal for a week or more. When the cause of the abnormal condition disappears, the centres are readjusted to the normal standard.

E. Post-mortem Rise of Temperature.

A rise of temperature after death is not uncommon ; indeed, in case of violent death of healthy individuals, and after death following convulsions, a rise in temperature is almost invariable. This increase is due to continued heat-production and to diminished heat-dissipation. Heat-production after death may be due to continued chemical activity in the muscles and other structures which are not dead but simply in a moribund state. There is, as it were, a residual metabolic activity which remains in the cells until their temperature has been reduced to such a standard that the molecular transformations cease—in other words, until the death of the cells occurs. Consequently, the higher the temperature of the individual at the time of somatic death (the cessation of the circulation and respiration), the longer heat-production continues, because the longer the time required to cool the cells to such a degree that their chemical processes no longer go on. Heat is also produced during the development of rigor mortis. The more quickly rigor sets in, and the more intense it is, the greater is the abundance of heat produced.

The tendency to an increase of bodily temperature is favored by the marked diminution of heat-dissipation which occurs immediately upon the cessation of of the circulation and respiration. Therefore, while both heat-production and heat-dissipation fall at once and enormously at the time of death, heat-dissipation may be decreased to a more marked degree than heat-production, so that heat may accumulate and the bodily temperature rise.

Temperature Sense.—(See Cutaneous Sensibility, in the section on Special Senses.)

X. CENTRAL NERVOUS SYSTEM.

INTRODUCTION.

The Unity of the Central Nervous System.—The human nervous system is formed by a mass of separate but contiguous nerve-cells. As each nerve-cell is always in close relations with some other nerve-cell, this system differs from those formed by the bones, muscles, or glands, since these tissues are distributed through the body in masses more or less isolated. Isolated groups of nerve-cells do not occur. Indeed a group of nerve-cells disconnected from the other nerve-tissues of the body, as the muscles or glands are disconnected, would be without physiological significance. It is desirable, therefore, to emphasize the fact that by dissection the nervous system is found to be continuous throughout its entire extent.

Subdivisions Artificial.—When, therefore, the nervous system is described as formed of a central and a peripheral portion, and the peripheral portion is further analyzed into its spinal and sympathetic components, the parts distinguished are found to have no sharply marked boundaries separating them, but really to merge one into the other.

The convenience of these subdivisions is undoubted, but the physiological processes which it is our purpose to study, overstep in so large a measure such conventional limits, that the picture of events in the central nervous system would be very incomplete, should they be traced only within such prescribed anatomical boundaries.

By virtue of its continuity, the nervous system puts into connection all the other systems of the body. Conforming as it does in shape to the framework of the body, its branches extend to all parts. These branches form pathways over which nerve-impulses travel toward the central system—the brain and spinal cord, enclosed in the cranial cavity and vertebral canal—and in consequence of the impulses that come in, there pass out from the central system other impulses to the muscles, glands, and blood-vessels.

All incoming impulses must reach the central system. Most important in this arrangement is the absence of any device for short-circuiting the incoming impulses. It is a fact of the greatest significance, that until they have entered the central system the incoming impulses do not give rise to those outgoing, and thus all incoming impulses are first brought to the spinal cord and brain, and the outgoing impulses are there aroused and co-ordinated by them.

By means of the central system there are established reactions in those tissues not directly affected by the variation of the external conditions, and thus

there follows an amount and variety of response in the organism as a whole out of all proportion to the strength of the physical stimuli employed. Owing also to the wide connections of the nervous system and the conduction of all incoming impulses to its central part a measure of harmony is maintained between the various activities of the several systems composing the body. Thus not only the various systems forming the body are in this manner controlled, but the body as a whole, in relation to all things outside of it and forming its environment, is even more plainly under the guidance of these administrative cells.

Growth and Organization.—In this connection, it is fitting to emphasize a character of the central system which is both unique and highly important. The physiological connections existing between the nerve-elements in youth are very incomplete and poorly established, more so than in any other system of the body; in the history of the growth of the nervous system, the increase in weight and change in shape run parallel with an increase in its organization—*i. e.* in the connections between its constituent cells. This organization results in better and more numerous physiological pathways which permit the system, as a whole, not only to do more perfectly at maturity those things which it could do in some degree at an earlier age, but also, by virtue of its increased complexity, to do at maturity those things which previously it could not do at all.

Growth in the case of this system implies, therefore, an increase in complexity such as nowhere else occurs, and since this growth can be modified by the experience of the individual during the growing period, the importance of understanding it and its relation to organization is evident.

Phenomena Involving Consciousness.—It is with the nervous system that the phenomena of consciousness are most closely linked. Strictly, physiology concerns itself at present with the reactions of the nervous system, which can be studied without an appeal to consciousness. A moment's consideration shows, however, that in the physiology of the brain the assistance to be obtained by passing beyond the limit thus laid down is of more value than any boundary, and hence, although the field of consciousness is sacred to psychology, physiology should not be deprived of any of the advantages which come from the privilege of occasional trespass.

Plan of Presentation.—In accordance with these facts, it has seemed best to first present—

Part I. The physiology of the nerve-cell, considered as a peculiar kind of tissue-element, endowed with special physiological characters.

Part II. The activities of the simplest groups of these elements. The physiological grouping is of course mainly dependent on the anatomical arrangement, and, as must always be the case, the activities of one group modify those of others. Stated in general terms, the problem in this part is that of *the pathway of any impulse through the central system.*

Part III. The reactions of the system taken as a whole. Here its capabilities as a unit are contrasted with those of the other tissue-systems, and its

growth, organization, and rhythms of rest and activity, are more properly presented as functions of all its parts than as functions of special subdivisions.

PART I.—PHYSIOLOGY OF THE NERVE-CELL.

A. Anatomical Characteristics of the Nerve-cell.

Form of Nerve-cells.—Morphologically, the mature nerve-cell is regarded as composed of a cell-body, containing a nucleus together with other modified inclusions and possessed of one or more outgrowths or branches. Some of these branches may be very long, such for instance as those which form nerve-fibres; other branches are short and differ from the nerve-fibres in their structure.

The terms employed in describing the nerve-elements are as follows: To the entire mass under the control of a given nucleus and forming both cell-body and branches, the term *nerve-cell* is applied. The inclusions within the cell-body have the usual designations. Nerve-cells differ greatly in the number of the branches arising from them. In some cells there appear to be two nerve-fibres arising from the cell-body, in others only one. For convenience the description about to be given will apply to the latter group only. From most cells there arises one principal branch, which when considered alone is described as a nerve-fibre, but when considered as the outgrowth of the cell-body from which it originates, is called a *neuron*.[1] Cells with one neuron are called mononeuric. Cells with two neurons, dineuric. The neuron, in many cases, has branches, both near its origin from the cell-body and also along its course. These branches are designated as *collaterals*. Contrasted with this principal outgrowth are the other branches of the cell,
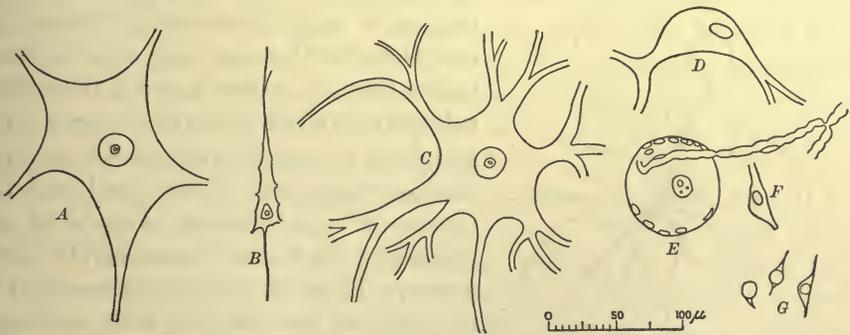
FIG. 143.—A group of human nerve-cell bodies, drawn to scale; × 200 diameters: *A*, cell-body from the ventral horn of the spinal cord, longitudinal section; *C*, the same, transverse section; *B*, cell from the third layer of cerebral cortex; *D*, cell from the column of Clarke; *E*, cell from the ganglion of the spinal nerve-root, with neuron; *F*, "solitary" cell from the dorsal horn of the spinal cord; *G*, granule from the cortex of the cerebellum (modified from Waller, *Human Physiology*).

which are individually much less extensive and which divide dichotomously at frequent intervals. From the tree-like form which they thus acquire they have been designated *dendrons*.

The accompanying illustration (Fig. 143) shows the features just described and also gives some idea of the variations in the size of the cell-bodies as found

[1] Schäfer, *Brain*, 1893.

in man. The nerve-cell body is usually ovoid in shape, although this type is much modified in many cases. As will be seen from Figure 143, the diameters of nerve-cells range from 10–100 μ,[1] and in some instances, in the spinal cord, cells of even larger diameter are found.

The Structure of the Nerve-cell Body.—Nissl[2] has shown that in nerve-cells hardened in strong alcohol there are two substances—one which is not stained by a basic aniline dye, and the second which is. The first forms a framework continuous with the fibrillæ of the nerve-fibre and enclosing the stainable substance in its meshes in small masses or granules. These granules are physiologically very sensitive, and the study of them under a variety of conditions has already revealed changes in the nerve-cells where none had previously been found.

Peculiarities of Nerve-cells.—As compared with the other cells of the body, the best developed nerve-cells are of large size, but the nucleus, proportionately to the cell-body, is not large, its value decreasing, as a rule, with the increase in the size of the entire cell. The most striking feature of the nerve-cell, however, is the great length to which its chief branch, the neuron, may attain, for in no other tissue does anything like so great a proportion of the cell-substance occur as a branch. The form of cell represented in Figure 144 is one in which the neuron shows a very short stem between the cell-body and its terminal twigs. In such an instance the entire extension of the neuron may be less than a millimeter. With this are to be contrasted those forms in which the neuron is very long and its mass great. What its greatest length may be is easily determined. Within the central system there are cells whose neurons extend from the cerebral cortex to the lumbar enlargement (60 centimeters), and again in the peripheral system there are cell-bodies in the lumbar enlargement of the spinal cord the neurons of which extend to the skin and muscles of the foot a distance of 100 centimeters. These are the extreme cases, but as the neurons are distributed to all intermediate points both in the central and peripheral system, every intermediate length between these and the cells with very short neurons previously mentioned, is to be found.

FIG. 144.—A cell with a short neuron giving off many branches. In such a cell the neuron is less in volume than the cell-body. This is the extreme form of the "central cell" (Ramón y Cajal). *D*, dendrons; *N*, neuron.

Volume Relations.—Calculation shows that the volume of the cell-body of a pyramidal cell in the human cerebral cortex having a basal diameter of

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[1] $\mu = 0.001$ of a millimeter.

[2] *Allgemeiner Zeitschrift für Psychiatrie*, 1896, Bd. lii. S. 1147. (A condensed statement of previous work.)

16 μ, is, when calculated as a cone, approximately 4266 cubic μ. The neuron from such a cell would have a diameter of at least 2 μ, the medullary sheath being included. This gives an area for the cross section of the neuron, of 6.3 square μ. Thus in the case chosen a portion of the neuron 680 μ long would have a volume equal to the cell-body. We may assume this neuron to be 15 centimeters = 150,000 μ long. Dividing the entire length of the neuron by the length of the piece having the volume of the cell, it appears that the volume of the neuron is 220 times that of the cell-body.

Repeating the same process with a cell from the lumbar enlargement of the spinal cord, taking a medium cell with a diameter of 46 μ and a volume (calculated as a sphere) of 50,000 cubic μ, a neuron with a diameter of 10 μ, and a length of 100 centimeters, the relation of the volume of the neuron to that of the cell-body is 1570 to 1.

This estimate of the volume of the neuron includes, in addition to the axis-cylinder, the enclosing medullary sheath. The volumes of these two portions are approximately equal, so that either the axis-cylinder or the medullary sheath exceeds the cell-body in volume about half as many times as does the entire neuron. It is extremely difficult to estimate the mass of the dendrons. In some instances, as in the cells of the spinal ganglia (Fig. 147) they are absent, while in the large cells of the cerebellum—Purkinje's cells—they form a mass which must be many times greater than that of the cell-body proper. In most cells, however, the dendrons have at best a mass several times as great as that of the cell-body.

Size of Nerve-cells in Different Animals.—In discussing the size and form of cells in man it becomes of interest to determine how far the observations apply to the lower mammals. The facts are briefly these : It can be said that the smaller mammals usually have the smaller nerve-cells, but the decrease in the mass of the nerve-cells is not proportional to the decrease in the mass of the entire body. For example, Kaiser[1] has shown that the cell-bodies occupying the ventral horn in the cervical enlargement of the spinal cord of the bat, the rabbit, and the monkey are in many cases as large or larger than those found in man.

Size of the Neurons in Different Animals.—Though the volume of the cell-body and the *diameter* of the associated neuron are approximately similar in any two animals of different size, as for instance in a bat and in man, it is also evident that the neuron could nevertheless not have the length in the bat that it does in man, and that in this last dimension at least there is a diminution corresponding to the size of the animal. Nevertheless, the volume of the entire cells—cell-body plus neuron—still remains *proportionately* very large in the smaller mammals.

The bearing of this fact on the comparative physiology of the nervous system is evident, for, under these conditions, as the volume of the entire nervous system is diminished, the number of cell-elements constituting it must also be

[1] *Die Funktionen der Ganglienzellen des Halsmarkes*, Haag, 1891.

diminished, and thus the structure of this system in the smaller mammals becomes numerically simplified.

Size and Function.—Histology shows us the nerve-cell prolonging itself into branches often much subdivided, the dendrons and the neuron. Such a cell contains a mass of living substances capable of being broken down and built up chemically, and there is nothing against the inference that the larger the cell the greater is the quantity of these living substances, and hence the larger the amount of stored energy represented by it. The larger cells are therefore those capable of setting free the greater amount of energy. The energy-producing changes are in the greatest measure to be associated with the cell-body, rather than with any of the branches. On the other hand, the nerve-cells with large cell-bodies, sending out as they do branches which are more voluminous than those nerve-cells that are small, furnish a greater amount of material to form the ultimate twigs into which these branches finally split. From this it follows that in general the large nerve-cells have more points of connection with the structures about them, as well as the capacity for the liberation of a greater amount of energy.

Growth of Nerve-cells.—During growth and development the nerve-cells may present many changes in appearance (Fig. 145).

The nerve-elements are derived from germinal cells found in the epiblast of the embryo. Amid the columnar epiblastic elements forming the medullary tube these spherical cells appear in man about the third to the fourth week of fetal life.[1] They divide rapidly and in such a way that one daughter-cell continues as the germinal cell, while the other moves away from the primitive surface of the body and becomes without further division a young nerve-cell or *neuroblast*. The formation of neuroblasts in man ceases or becomes very slow and unimportant by the end of the third month of fetal life.

FIG. 145.—Portion of developing medullary tube (human) seen in frontal section × 1100 diameters (His): *G*, germinal cell; *N*, neuroblasts.

Two characters of the neuroblast are worthy of careful consideration. First, there is good indirect evidence that, in early life at least, and before their branches have been formed, they are migratory, moving in an amœboid manner. This being so, the perfection with which they arrange themselves in the adult system depends on the accuracy with which they respond to those conditions that determine their migration as well as upon the normal character of these directing influences (mechanical strain;[2] chemotaxis or nutritive attrac-

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[1] His: *Archiv für Anatomie und Physiologie*, Anat. Abthlg., 1889.
[2] His: *Unsere Körperform*, 1874.

tion).[1] But with so much liberty of movement and with directing influences that are so complicated, the chances for deviation from a fixed arrangement are much enhanced.

Polarization of Neuroblasts.—Moreover, very early in the history of the neuroblast the point on the cell-body from which the neuron will grow appears in many cases to be fixed, and the cell is thus physiologically polarized.[2] This polarity being established, the direction in which the neuron first grows is determined, and where the cells are misplaced this polarization can lead to the confusion of arrangement found in the brains of some congenital idiots.[3]

The volume of either the germinal cell or of the first form of the neuroblast was found by His[4] to be 697 cubic μ in a human fetus (embryo R–length 5.5 millimeters, aged 3 to 3.5 weeks). It has previously been shown that the volume of a spinal-cord nerve-cell is, taken altogether, 78,500,000 cubic μ, and that of this the neuron occupies 78,450,000 cubic μ, and the cell-body 50,000 cubic μ. If we take *half* of this total volume, it gives under the conditions chosen an increase in volume between the neuroblast and the mature cell of 57,456-fold.

Maturing of the Nerve-cell.—The maturing of the nerve-cell involves several changes. First, the outgrowth of the neuron or neurons; next, the formation of the dendrons; and finally, in some cases, the medullation of the neuron, while simultaneously and with greater or less rapidity the absolute amount of substance in both cell-body and neuron is being increased, together with a chemical differentiation of the contents of the cytoplasm and the nucleus. The time in the life-history of the individual at which these several events occur is variable, and may be delayed beyond puberty at least, while the rate at which they occur is different in different cases. Furthermore, many nerve-cells never develop beyond the first stages of immaturity (Fig. 146).

Form of the Neuron as a Means of Classification.—Of the various devices used to classify nerve-cells, the form of the neuron is the most useful.

Physiologically, the nerve-cell is significant as a pathway for the nerve-impulse. The current conception of the change called the nerve-impulse is that it begins at one point of the cell and travels from there to the other parts; one of the other parts is the neuron, and along this the impulse can be shown to pass. Although it cannot be directly demonstrated, there is reason to think that primitively all the branches of a cell had similar physiological powers. Indeed, the nerve-cell body stimulated at any point may be responsive just as an amœba is responsive at any portion of its surface. When, however, the branches are formed they become the channels through which the impulses pass, and hence assume a special significance without indicating any fundamental change in the structure of the cell. Where the cell has well-developed

[1] Davenport: *Bulletin of the Museum of Comparative Zoology*, Harvard College, Nov., 1895; Herbst: *Biologische Centralblatt*, 1894, Bd. xiv.

[2] Mall: *Journal of Morphology*, 1893, vol. viii.

[3] Koster: *Neurologische Centralblatt*, 1889, Bd. viii.

[4] *Archiv für Anatomie und Physiologie*, 1889.

branches we expect an arrangement of them such that the impulse shall enter the cell-body by one branch and leave it by another.

On examining the mature nerve-cells of man with this idea in mind, two types are found. The first type may be exemplified by the pyramidal cortical

Fig. 146.—*A–D*, showing the phylogenetic development of mature nerve-cells in a series of vertebrates; *a–e*, the ontogenetic development of growing cells in a typical mammal; in both cases only pyramidal cells from the cerebrum are shown; *A*, frog; *B*, lizard; *C*, rat; *D*, man; *a*, neuroblast without dendrons; *b*, commencing dendrons; *c*, dendrons further developed; *d*, first appearance of collateral branches; *e*, further development of collaterals and dendrons (from S. Ramón y Cajal).

cells shown in Figure 146. Here, from a pyramidal body (*D*) there arise a number of dendrons, while from the lower portion of the cell the neuron grows out and branches. In the other type the neuron alone grows out. Its branches
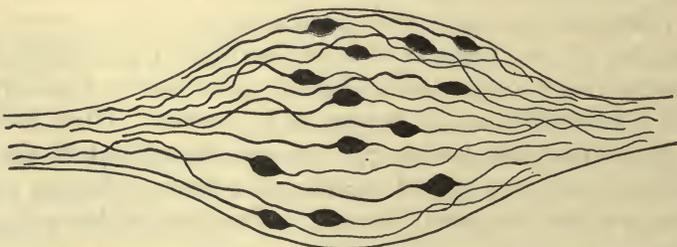
Fig. 147.—Spinal ganglion of an embryo duck; composed of dineuric nerve-cells (van Gehuchten).

are but two in number and both are medullated. They pass in opposite directions and in this type there are no dendrons. To understand the arrangement in these cases, recourse must be had to the facts of development. The second

type begins its development as a bipolar cell, a neuron growing from each pole (Fig. 147). In the adult spinal ganglion of the higher mammals, however, no such bipolar cells are to be found, but only cells having a single neuron which soon divides into two branches.

Figure 148 beautifully illustrates the phases of this change as seen in a single section. At first one neuron arises from each pole of the ovoid cell-body. Later the cell-body occupies a position at the side of the two neurons, which appear to run into one another. Finally the cell-body is separated from the two neurons by an intervening stem. The stem has the characters of a nerve-fibre and from the end of it the original two neurons pass off as branches.

From this mode of development it is plain that the single stem must be looked upon as containing a double pathway, although it appears to be in all ways a single fibre, for on the one hand it contains the path for the incoming and on the other for the outgoing impulses. Recent investigations have shown in a striking way that cells modified in this manner are by no means limited to the spinal ganglia, but occur in the cortex of the cerebellum and elsewhere. The study of this modification brings with it the following suggestion: If the single stem in the modified spinal ganglion-cells must

FIG. 148.—Dineuric changing into mononeuric cells: from the Gasserian ganglion of a developing guinea-pig (van Gehuchten).

by virtue of its development contain a double pathway, it is fair to inquire whether the same may not be true of the other forms of the nerve-cell in which the neuron also appears to be single. Among the cortical cells the arrangement of the branches is such that, for aught that is known, the stem of the neuron may functionate in the manner suggested, and contain more than one pathway.

Classifying the nerve-cells, therefore, in the light of these facts, we find— (1) The pyramidal type, in which the dendrons and neuron are both well developed, and in which the greater part of the impulses most probably enter the cell by way of the dendrons and leave by way of the neuron; (2) The spinal ganglion type, in which originally the impulse passes in at one pole of the cell and out at the other, but in the course of development the *two* neurons become attached to the cell-body by a single stem, and by inference there must be in this stem a double pathway. In this special case there are no dendrons.

Growth of Branches.—After the cells have taken on their type form, the branches still continue to grow, not only in length, but in diameter. In man, for example, the diameter of the nerve-fibres (neurons) taken from the peripheral nerves at birth is 1.2–2 μ for the smallest, up to 7–8 μ for the largest, with an average of 3–4 μ, while at maturity it is 10–15 μ for the larger fibres.[1]

In the second spinal nerve of the frog, Birge found the fibres[2] to increase

[1] Westphal: *Neurologische Centralblatt*, 1894, No. 2.
[2] Birge: *Archiv für Anatomie und Physiologie*, 1882.

in average diameter from 7.6 μ to 12.6 μ, as the total weight of the frog increased from 1.5 to 63.0 grams.

The branch which forms the neuron contains an axis-cylinder surrounded by a medullary sheath. There are two views concerning the constitution of the axis-cylinder—one [1] that the axis is composed of slender thread-like fibrillæ floating in a coagulable plasma, these fibrillæ being the conductors of the nerve-impulses. The opposing view is that advocated by Leydig,[2] Nansen,[3] and Schäfer,[4] to the effect that the axis-cylinder is formed by a spongy framework in the meshes of which is a semi-fluid plasma. According to this latter view the plasma is the substance through which the impulses pass. Neither view is beyond criticism, nor does either of them admit of detailed correlation with the physiological facts. The conception of the axis-cylinder as composed of fibrillæ appears at first sight to offer an anatomical arrangement for a number of isolated pathways within a single fibre, but the fibrillæ cannot be unbranched from one end of their course to the other, since many nerve-fibres near their final distribution divide a number of times, the diameter of the individual fibrillæ remaining the same; and the combined cross sections of the axis-cylinders in the subdivisions demand, therefore, a far greater number of fibrillæ than is contained in the main stem of the fibre. On the other hand, the conception of the axis-cylinder as a series of tubes interosculating at very acute angles does away at the start with any notion of structural isolation of the pathways within the fibres. This latter view is, however, the better supported histologically.

When the axis-cylinder increases in diameter, it must, under this view, be by the formation of more of these tubes, for their size, though variable, is not directly in proportion to the diameter of the fibre. While the neuron is growing as a naked axis-cylinder it is usually slightly enlarged at the tip (Cajal), suggesting that it is specially modified at that point. The nutritive exchange on which the increase of the entire neuron depends appears to take place along its whole extent, and not to be entirely dependent on material passed from the cell-body into the neuron.

Medullation.—After the production of its several branches the next step in the growth of the cell is the formation of the medullary sheath. Not all neurons have a medullary sheath, nor is any neuron completely medullated. In the sympathetic system there is a very large proportion of unmedullated fibres. In the central system the number is very large although their mass is small. Of the significance of the medullary sheath we know nothing. The suggestion that it acts to insulate the nerve-impulse within a given axis-cylinder has little or no evidence in its favor. The suggestion that it is nutritive is plausible, but important differences in the physiological reactions of the two classes of nerve-fibres have not yet been found.

In studying the effect of stimulation and of changes in temperature on the

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[1] Kuppfer und Boveri : *Abhandlungen d. k. bayer. Akad. den Wissenschaften,* München, 1885.

[2] *Zelle und Gewebe,* Bonn, 1885.

[3] *The Structure and Combination of the Histological Elements of the Central Nervous System,* Bergen, 1887.   [4] *Quain's Anatomy,* 10th edition, vol. i. pt. 2, 1891.

irritability and conductivity of nerve-fibres[1] it was found that certain nerve-fibres, notably the vaso-constrictor fibres and the sweat-fibres in the sciatic nerve of the cat, when they were subjected to a faradic current continued for several minutes, lost their irritability, completely or in part, at the point of stimulation. This "stimulation fatigue" is not known to be produced in nerves which are unquestionably medullated. It does occur where the nerves are unmedullated, but it also occurs where the absence of medullation has not been proved, and hence cannot be put forward as a differential character distinguishing these two sorts of nerves. The medullated neurons are in their early history unmedullated, and only later acquire this sheath, so that medullation might be taken to represent a final step in the highest development of the nerve-cell. The fact that certain groups of fibres are not functional till *after* they are medullated hardly bears on the question, for the following reason : Until a group of fibres has established a physiological connection with the tissues which it is to control, it cannot be expected to influence them, and it has yet to be shown that the appearance of functional activity and the beginnings of medullation are not both of them the result of such growth-changes at the distal end of the axis-cylinder. The changes involved in establishing physiological connections are those by which the tips of the branches formed by the neuron of one cell come into such relation with other branches of a second cell or some non-nervous tissue that the nerve-impulse can pass between them. At the same time the non-medullated neurons establish connections with the tissues controlled by them just as well as do those which are to be medullated, but why one goes on to the acquisition of the sheath and the other remains without it, is not explained. Neither is it known how far one of these forms may replace the other, although, it is not improbable that the proportions of medullated and unmedullated fibres in different persons may be very unlike.

Growth of Medullary Sheath.—Whatever may be the significance of the medullary sheath it is usually formed before the nerve-element as a whole has attained its full size. In the peripheral system it depends on the presence of cells which envelop the axis-cylinder, forming a tube about it. Each ensheathing cell is physiologically controlled by a nucleus which becomes situated about midway between its extremities. The cell-substance is largely transformed into myelin, and the line of junction between two of these sheathing cells forms a node of the nerve-fibre. In the sheath of a growing nerve-cell at least two changes are clearly marked : As the axis increases in diameter the medullary sheath becomes thicker. The change is such that in the peripheral system the areas of the axis-cylinder and of the medullary sheath as shown in cross sections remain nearly equal (Fig. 149). On the other hand the length of the internodal segments tends to increase with an increase in the diameter of the nerve-fibre, and for nerves of the same diameter it is less in man than in the lower mammals. In a given fibre the segments are shorter at the extreme peripheral end (Key and Retzius). In the young fibres, also, they are shorter and increase in length with age.

[1] Howell, Budgett, and Leonard: *Journal of Physiology*, 1894, vol. xvi.

A physiological significance attaches to these segments, because, as Ranvier long since pointed out, it is at the nodes that various staining reagents most easily reach the axis-cylinder. This suggests that normal nutritive exchanges may follow the same path and thus short internodal segments giving rise to many nodes would represent the condition most favorable to exchange between the axis and the surrounding plasma. Thus far, histological observation shows the more numerous nodes where the physiological processes are presumptively most active, and hence

Fig. 149.—Longitudinal (*B*) and transverse (*A*) sections of nerve-fibres. The heavy border represents the medullary sheath, which becomes thicker in the larger fibres. Human sciatic nerve. × 200 diameters (modified from van Gehuchten).

supports the hypothesis suggested. Cases of the interpolation of new sheathing cells to form additional segments between those originally laid down have also been described.[1]

Medullation in Central System.—Concerning the relation of the medullary sheath to the axis-cylinder in the central system, our information is less complete. The elements which give rise to the medullary substance are not known and the myelin is not enclosed in a primitive sheath. There are no internodal nuclei regularly placed, yet Porter[2] has demonstrated in both the frog and the rabbit the existence of nodes in fibres taken from the spinal cord. The conditions which there exist must be further studied before any general statements concerning the medullary substance in the nerve-centres can be ventured, yet it is an important observation, that whereas medullation in the peripheral system is mainly completed during the first five years of life, the process continues in the central system, and especially in the cerebral cortex, to beyond the thirtieth year.

Whatever views may be held concerning the capacities of a medullated fibre, it is to be remembered that the medullary sheath does not cover the first part of the neuron on its emergence from the cell-body, nor are ultimate branches of the neuron medullated in the region of their final distribution.

The acquisition of this sheath occurs in response to a physiological change that appears at the same time along the entire length of the fibre. The process, therefore, is not a progressive one, but practically simultaneous.

What has just been said applies to the main stem of the neuron. As shown in Figure 146, the neuron often has branches near its origin, and according to the observations of Flechsig[3] these may become medullated. Concerning the time of the medullation of these branches there are no direct observations, but if it is controlled by the same conditions which appear to control the process in the main stem, then, as the branches form their physiological connections later than the main stem, it would follow that their medullation should also occur later, and the studies on the progressive medullation of the cerebral cortex favor such a view.

[1] Vignal: *Archives de Physiologie,* 1883.   [2] *Quarterly Journal Microscopical Science,* 1890.
[3] *Archiv für Anatomie und Physiologie,* 1889.

Changes in the Cytoplasm.—While the nerve-cell is passing from the immature to the mature form, increasing in mass and in the number of its branches, as well as acquiring its medullary sheath, it is also undergoing various chemical changes. The chromatic substance in the cytoplasm becomes more abundant at maturity and the pigment-granules increase in quantity.[1]

Old Age of Nerve-cells.—But the nerve-cell, though possessing, in most cases, a life-history co-extensive with that of the entire body, eventually exhibits regressive changes. These changes of old age consist, in some measure, in a reversal of those processes most evident during active growth. The cell-body, together with the nucleus and its subdivisions, becomes smaller, the chromatic substance diminishes, the pigment increases, the cytoplasm exhibits vacuoles, the
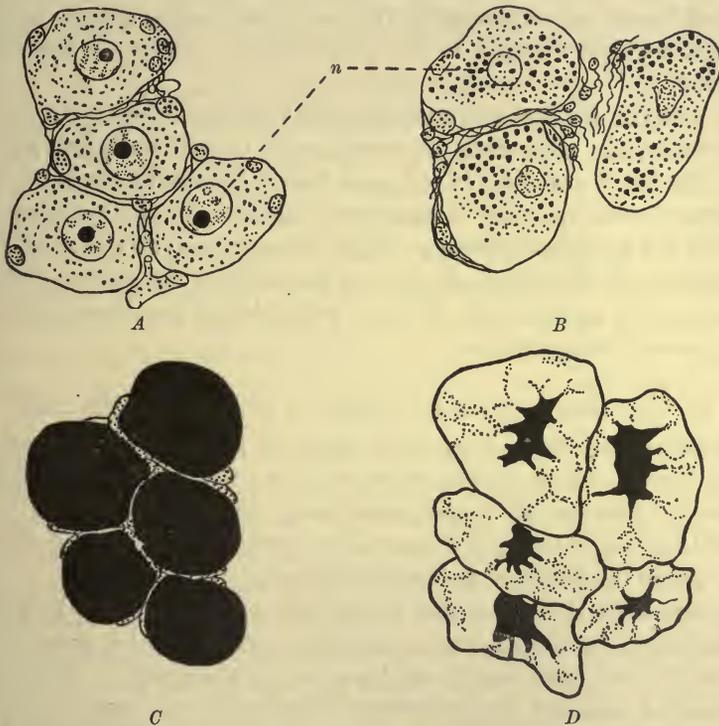
FIG. 150.—To show the changes in nerve-cells due to age: *A*, spinal ganglion-cells of a still-born male child; *B*, spinal ganglion-cells of a man dying at ninety-two years; *n*, nuclei. In the old man the cells are not large, the cytoplasm is pigmented, the nucleus is small, and the nucleolus much shrunken or absent. Both sections taken from the first cervical ganglion, × 250 diameters; *C*, nerve-cells from the antennary ganglion of a honey-bee, just emerged in the perfect form; *D*, cells from the same locality of an aged honey-bee. In *C* the large nucleus (black) is surrounded by a thin layer of cytoplasm; in *D* the nucleus is stellate, and the cell-substance contains large vacuoles with shreds of cytoplasm (Hodge).

dendrons atrophy, and the neurons also probably diminish in mass. In some instances the entire cell is absorbed. Some of these facts are illustrated by the observations of Hodge[2] on the spinal ganglion-cells of an old man of ninety-two years as compared with those of a new-born child (see Fig. 150). The

[1] Vas: *Archiv für mikroskopische Anatomie,* 1892.
[2] *Journal of Physiology,* 1894, vol. xvii.

changes in the outline of the nucleus are also to be noted, as well as the decrease in their volume. The figures for the decrease in the volume of the nucleus are given in the following table, showing the principal differences observed on comparing the spinal ganglion-cells (first cervical ganglion) from a child at birth with those from a man dying from old age at ninety-two years (Hodge):

	Child at birth; male.	Old man.
Volume of nucleus	100 per cent.	64.2 per cent.
Nucleoli visible	53 " "	5 " "
Deep pigmentation	0 " "	67 " "
Slight pigmentation	0 " "	33 " "

Analogous changes were found by this investigator in the antennary ganglia of old honey-bees as compared with the corresponding ganglia taken from those which had just emerged in the perfect form. These are also shown in Figure 150.

Since with the chemical and morphological variations which occur during the entire growth-cycle there must go variations in the physiological powers, we are led therefore to anticipate in old age a correlation, on the one hand, between the decrease in the quantity of functional substance in the cytoplasm and a decrease in the energy-producing power of the cells, and, on the other, between the absorption of the cell-branches and a limitation in the extent of the influence exercised by a given cell. Both of which defects are characteristic of the nervous system during old age.

B. The Nerve-impulse within a Single Nerve-cell.

The Nerve-impulse.—Nerve-cells form the pathways along which nerve-impulses travel. As introductory, therefore, to the study of the composite pathways in the central system, comprising as they do several elements arranged in series, it becomes important to study the behavior of the nerve-impulse within the limits of a single cell-element.

Experimentally it is found that the nerve-impulse is revealed by a wave of molecular change in the form of an electrical variation which passes along the nerve-fibre in both directions from the point of stimulation. Under normal conditions the intensity of the electrical change does not vary in transit, but it does change with changes in the strength of the initial stimulus. It moves in the peripheral nerves of the frog in the form of a wave some 18 millimeters in length, at the mean rate of 30 meters per second, and this rate can be somewhat retarded by cooling the nerves, and accelerated by warming them. In mammals, the rate in the peripheral nerves has been found by Helmholtz and Baxt to be 34 meters per second. The nerve-impulse can be aroused at any point on a nerve-fibre provided a sufficient length of fibre be subjected to stimulation. Mechanical, thermal, chemical, and electrical stimuli may be used to arouse it, but just how the impulse thus started differs from that normally passing along the fibres as a consequence of changes in the cell-bodies of which these fibres are outgrowths is not known. It appears, how-

ever, that the impulses roused by artificial stimuli are usually accompanied by a much stronger electrical variation than accompanies the normal impulses.

In the peripheral system the nerve-impulse, when once started within a fibre, is confined to that track and does not diffuse to other fibres running parallel with it in the same bundle. In other words, throughout this portion of its course the conduction of the impulses is isolated.

The above-mentioned facts have been observed on the peripheral nerves, and these morphologically are but parts of the medullated neurons, the cell-bodies of which are located either in the central system proper or in the spinal or sympathetic ganglia.

The observations apply therefore to but one portion of the nerve-cell, and our present purpose is to determine how far it is possible to extend them so that they apply to the entire nerve-cell, noting at the same time the modifications introduced by this extension.

Conditions Surrounding the Extension of the Nerve-impulse.— Owing to the small size of nerve-cell bodies, there are of course very few instances in which a *single* nerve-cell, or part of such a cell, has been the object of direct physiological experiment.

Groups of elements are usually employed like those represented in the groups of neurons forming the various peripheral nerves, and where these have common functions, the inference may be made from the changes in the mass to changes in the constituent units. This method can be used without serious error, and it is possible, therefore, to speak of events occurring in the individual elements, although the experiments were made upon masses of them.

Direction of the Nerve-impulse.—In the case of a given nerve-cell, the impulses which we usually consider pass in one direction only. For instance, along the ventral nerve-roots of the spinal cord the impulses pass from the cord to the periphery, while in the dorsal roots, so far as they take origin from the cells of the spinal ganglia, these impulses travel in the opposite direction. At the same time experiment has shown that if a nerve-trunk be stimulated at a given point, then the nerve-impulse can be demonstrated as passing away from the point of stimulation in *both* directions.

We are therefore led to inquire what limits are set to the passage of impulses in a direction opposite to the usual one. The narrowest limits, it appears, are those of the single cell in which the impulse has originated. The experimental observations are as follows : When the fibres forming the ventral root of the spinal cord are stimulated electrically, and the cross section of the cord, somewhat cephalad to the level at which the root joins it, is explored with an electrometer, there is not found any evidence of nerve-impulses passing cephalad in the substance of the cord. The arrangement of the cells in the cord is such, however, that the cell-bodies which give origin to the fibres forming the ventral root are physiologically connected with fibres running toward them from every portion of the cord, and under normal conditions these fibres convey impulses *to* them. The experiment shows that when, under

the conditions named, an impulse enters the cell-body by way of the ventral root-fibre to which it gives origin, it does *not* pass out of this cell-body into the other elements of the cord causing an electric change detectable as a negative variation. It appears, therefore, that the connection between the fibres of the cord and the cell-bodies in question is such that though impulses readily pass from the former to the latter, they do not pass in the reverse direction, thus showing that in this instance the cell-boundary sets a limit to the reversed impulse.[1]

With the elements forming the dorsal spinal root, the case is at first glance apparently different, though in reality it is the same. These elements are those having the cell-body located in the spinal ganglion. The cells are essentially dineuric (Fig. 148); one neuron extends from the point of division toward the periphery, and the other enters the spinal cord to distribute itself as a fibre coursing longitudinally for some distance within it (see Fig. 151). The normal direction of the effective impulses is from the periphery toward the cord, and within the cord they are delivered to other elements which carry them in all directions. It is therefore to be expected that the stimulation of the dorsal root-fibres would give rise to impulses passing in both directions in the dorsal columns of the cord. When, however, the dorsal columns of the cord are electrically stimulated in a cross section made just above the level of the entrance of a dorsal root, then it is found that the electrical variation is to be detected in the nerve-fibres on the distal side of the spinal ganglion. These impulses have therefore passed in a direction the reverse of that usually taken. The fibres which are stimulated in this instance in the cross section of the cord are, however, outgrowths of spinal ganglion-cells, and thus, although the stimulation of the cord does give rise to an impulse in the peripheral nerve, nevertheless the impulse is continually within the limits of one cell-element. The question of whether the reversed impulse can traverse the cell-body is here answered in the affirmative, for these cells are virtually dineuric, and everything points to the passage of the impulse *through* the cell-body in passing from one neuron to the other. There is, however, no evidence that the stimulation of the dorsal columns of the cord

FIG. 151.—A longitudinal section of the cord to show the branching of incoming root-fibres in dorsal columns. At the left are three *D R* root-fibres, each of which forms two principal branches. These give off at right angles other branches, collaterals, *Col*, which terminate in brushes. *C C*, central cells, whose neurons give off similar collaterals (Ramón y Cajal).

[1] Gotch and Horsley : *Proceedings of the Royal Society,* 1888.

produces outgoing impulses in the dorsal nerve-roots except when the stimulus is applied to the neurons which are outgrowths of the cells of the dorsal ganglia.

Arrangement in the Central System.—As will be shown later on, there is reason to picture the passage of the nerve-impulse through the central system as accomplished by a series of relays in which each cell-body is roused to discharge its own impulse as the consequence of an impulse received from some other cell.

When therefore an impulse is brought by one neuron to a cell-body, and passed on by way of it to another neuron which is a part of the stimulated cell, there is no escape from the conclusion that, if in this case the cell-body is physiologically significant, it rather originates the impulse which traverses the second neuron than acts merely as the conductor for it.

This is suggested by the changes caused in the cell-body as the result of stimulating it. At the same time there is an appreciable delay (0.036 second) in the passage of the nerve-impulse through the cell-body in the case of those cells which form the spinal ganglion.[1]

Double Pathways.—If the view is correct, that in passing through the spinal ganglion the impulse enters the cell-body, then the nerve-impulse passes to and fro along the common stem which joins the cell-body with the two neurons (*vide* Fig. 148). In such a case, the impulse going toward the cell must travel either through the entire stem, or through a part of it only. This stem is conceived as homologous with the bases of the two neurons which originally arose from the dineuric cell, thus morphologically representing a double pathway, although in the mature cell there is, from the histological side, absolutely no trace of this duplicity.

The same arrangement must exist in the case of cells like those represented in Figure 152, in which the neuron arises from the base of a dendron at some
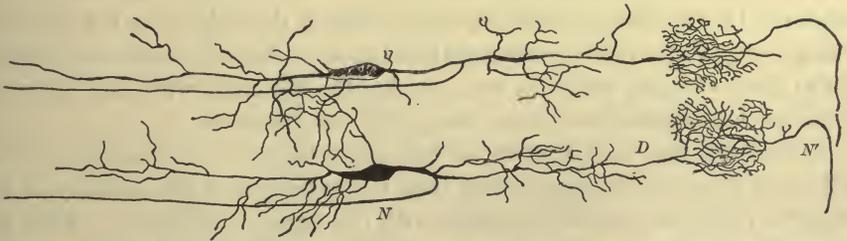
FIG. 152.—Showing the relations between the terminal branches of the dendrons (*D*) and of the neurons (*N*) of the optic fibres where they come together in the superficial layer of the optic lobe of the chick; also showing the origin of the neuron (*N*) from a dendron (van Gehuchten).

distance from the cell-body, and in which nerve-impulses arriving over the dendron and leaving by the neuron must follow the portion of the cell-branch which is common to both, passing along it first in one direction and then in the other. It appears not improbable, therefore, that some outgrowths of the cell-body which morphologically are simple, really contain more than one physiological pathway.

[1] Gad and Joseph: *Archiv für Anatomie und Physiologie*, 1889.

Significance of Shape.—Since the outgoing nerve-impulses pass along the efferent cell-branches to their tips, it follows that if the impulses are destined to leave the cell limits they will do so at the extremities of the branches. This leads to the question how far the possession of branches is necessary to the functional activity of a nerve-cell either for the reception or transmission of an impulse. Since it has been pointed out that the spinal cord of the newt and fish [1] is capable of conducting impulses even before the dendrons of the cells composing it are developed, it follows that the transmission of impulses is in some way dependent on the condition of the cell-wall independent of cell-branches. This modification of the cell-wall may exist at points where there are no branches, or during this early period be a general property of the wall and only later become the peculiar property of that portion which forms the tips of the branches. But not only the capacity to receive, but also the capacity to deliver impulses is a function of the ends of the branches, and the cell-wall at these points must therefore be peculiarly modified with a still further differentiation determining the direction in which the impulses may pass. If, therefore, the mature cell is thus arranged, its shape and the number of its branches have a meaning. Each dendron represents at least one pathway by which impulses reach the cell-body. If, then, there are many dendrons, the cell-body is subject to a more complicated series of stimuli than if the branches are few. It will be remembered that the young nerve-cell has no dendrons, that the first branch to be formed is the neuron, and that the completion of the full number of dendrons is a slow process. The pathways formed by the dendrons are, therefore, continually increasing up to maturity.

Effect of Impulses.—The impulses which arrive at the cell-body produce there chemical changes. These changes when they reach a given volume and intensity cause a nerve-impulse which leaves the cell-body by way of the neuron. If the nerve-impulse is, as we assume, dependent on the chemical changes occurring in the cytoplasm, then the nerve-impulse must vary according to these changes, which in turn can hardly be similar when the incoming impulses that arouse them arrive along different dendrons.

Concerning the modifications in the nerve-impulse as dependent on the cell-body, there are thus far known only the variations in the intensity of the negative variation, this being greater with the stronger stimulus. When the nerve-impulses leave a cell-body after momentary stimulation, they depend not upon a single event but a series of events, varying slightly for the different groups of cells. Experiments showing the multiple character of the impulses aroused within the central system have been made by Gotch and Horsley.[2] When the motor cortex of a monkey was stimulated (Fig. 153) by means of the faradic current, the muscles which by this means were made to respond showed a long tonic contraction followed by a series of shorter clonic ones (Fig. 154, *D*). When the spinal cord had been cut across, the cortex was

[1] His: *Archiv für Anatomie und Physiologie,* 1890.
[2] *Proceedings of the Royal Society,* London, 1888.

again stimulated and the changes in the fibres of the cord which convey the impulses from the cortex to the spinal centres were investigated by means of the capillary electrometer. By this means a curve (Fig. 154, *D*) was obtained as a record of the negative variations passing along these fibres. This latter curve corresponds with the record for the muscular contraction and hence the relation between the two series of events is evident. It appears, therefore, that the cortical cells after the cessation of the stimulus still continue to discharge in a rhythmical manner. The attempt was also made to determine the rhythmic character of the negative variations in the motor nerve-trunk between the cord and the contracting muscle, but the changes there present, though sufficient to cause contractions of the muscle, were not strong enough to be recorded by a delicate capillary electrometer. This result suggests that the impulses sent out from the spinal cord by the normal discharge of the motor nerve-cells in it may differ from the impulses artificially aroused in the lesser intensity of the electrical changes that accompany them. The rate at which the nerve-cells discharge, as shown by the number of impulses which produce tetanus of a muscle indirectly excited, either by artificial stimulation of the nerve-elements in animals or by voluntary impulses in man, is about ten per second. It appears that at least the cortical cells and those of the spinal cord have the same rate of discharge, and that this rate is the same in some mammals (dogs, cats, rabbits, and monkeys) as in man. Hence a tendency to discharge about ten times a second may be assumed as characteristic of the mammalian nerve-cell.[1]

Fig. 153.—Schema illustrating the experiment for determining the number of separate nerve-impulses passing down the spinal cord upon stimulation of the cortex (from experiments on the monkey; Horsley): *E, E,* electrodes, intended to be on the "leg area." Where the cord is interrupted one non-polarizable electrode is placed over the cut end of the pyramidal fibres going to the lumbar enlargement; the other, on the side of the cord. These lead to the capillary electrometer, in which the column of mercury moves each time an impulse passes.

[1] Schäfer and Horsley: *Journal of Physiology*, 1885, vol. vii. Schäfer: *Ibid.*

Points at which the Nerve-impulse can be Aroused.—It appears probable that the excitation of any part of a nerve-cell is capable of producing
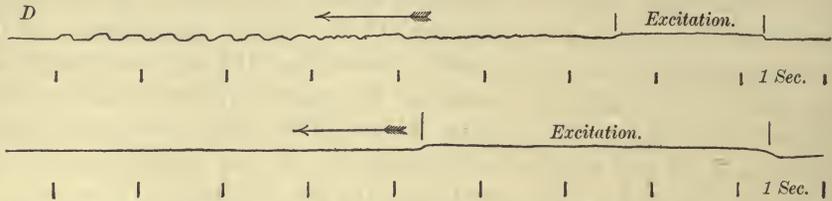
FIG. 154.—From a photographic record of the movements of the column of mercury in a capillary electrometer (Gotch and Horsley). The arrow shows the direction in which the record is to be read. The upper curve (*D*) shows the period of excitation by the interrupted current; this is followed by a series of waves in the record showing a number of separate impulses sent down from the cortex after electrical stimulation has ceased. In the lower curve the exciting electrodes were applied to the white matter directly, the cortex having been removed. The record shows that in this case no impulses pass after the stimulation has ceased.

a nerve-impulse, whether the stimulus be applied at the tips of the dendrons or to the neuron in its course.

There is, however, no indisputable evidence that within the central nervous system the cell-bodies of nerve-cells can be made to discharge by the direct application of electrical or other artificial stimuli to them, for there is no locality suited for such isolated stimulation. In every place where such cell-bodies are found they always lie more or less imbedded in the terminals of neurons that have originated elsewhere, and hence present methods are not fitted to decide whether the impulse is aroused in these cases indirectly by the stimulation of the terminals or directly by the passage of the stimulus through the cell-body alone. That artificial stimuli do in some way arouse the cell-bodies to discharge is amply shown by the fact that when the cortex is stimulated under the conditions just mentioned, the impulses continue to come from the cortex after the stimulus itself has ceased to act.

If after such a reaction the cortical layer containing the cell-bodies be cut away, exposing the cut ends of the fibres which have originated from them, and the stimulus be again applied, an impulse is to be detected in these fibres so long as the stimulation is continued, but the impulses cease when the stimulus stops. This difference in the time-relations and the form of the impulses according to the presence or absence of the cortical layer is taken as an indication that in the first instance the cell-bodies were stimulated, but it still leaves the question of directness of the stimulation undecided.

Probably every nerve-element in all its parts is to some degree irritable, and the reports to the effect that the cell-bodies cannot be directly stimulated are not supported by satisfactory proof that no nerve-impulses passed from the point to which the stimulus was applied.

Irritability and Conductivity.—In general, parts of the system which are irritable are also conductive, but there are special cases in which the irritability of the nerve-fibre can be distinctly separated from its conductivity, the latter being present while the former is absent.

It is an old observation that on stripping down the phrenic nerve by com-

pressing it between the thumb and forefinger and sliding these along the nerve, a contraction of the diaphragm is caused. The part of the nerve thus stimulated is soon exhausted. If, now, the same operation is repeated on a portion of the nerve lying nearer the spinal cord, contraction of the diaphragm again follows. This result was originally used to support the theory of a nerve-fluid, and was held to demonstrate that after the nerve-tubes in the portion of the trunk compressed had been emptied so that no reaction followed further pressure, then if the pressure were applied still nearer the cord the fluid from that part of the nerve could be driven forward and a contraction of the diaphragm would result. The notion of a nerve-fluid in the sense in which that term was used by the earlier physiologists has long since been abandoned, but for our purpose the experiment is important as showing that irritability and conductivity do not under such treatment disappear at the same time, but that the fibres remain conductive after they cease to be irritable, as is shown by the fact that the peripheral part of the nerve, though irresponsive, still permits the impulses aroused nearer the cord to pass through it.

It has been also shown[1] that in young regenerating motor fibres it often happens that while no response is to be obtained by the direct stimulation of the regenerated peripheral portion, yet the stimulation of the central and fully grown portion does cause a contraction of the muscles controlled by these fibres. In this case the newly formed fibres can conduct an impulse which gives rise to a contraction, although such an impulse cannot be aroused by directly stimulating them.

In the case of the cell-body certain conditions must be present in order that an impulse sufficient to cause an evident response shall be aroused. There is certainly no evidence that stimuli which for one reason or another do not cause such responses are without any effect whatever. At the same time all cases in which there may be marked delay in the response occur where the impulse passes from *one* cell to *another*, and hence the question can always be raised as to the exact point at which delay occurs.

Number of Stimuli necessary to Elicit a Response.—In an isolated portion of a nerve-cell, like a nerve-fibre for instance, a single stimulus is followed by a single nerve-impulse; on the other hand, the studies which have been made to determine the number of weak stimuli necessary to discharge a *series* of cell-elements indicate that there is a summation of stimuli, *i. e.* the discharge does not follow until a series of stimuli has been given. These experiments have been made for the most part with reflex frogs, and they indicate that with very weak stimuli that can be individualized, like mechanical impacts or single induction shocks, a given reaction can be obtained with remarkable regularity after a *given number* of stimuli, while the intervals between the single shocks may be varied within comparatively wide limits without modifying the number required.[2]

[1] Howell and Huber: *Journal of Physiology*, 1892, vol. xiii.
[2] Ward: *Archiv für Anatomie und Physiologie*, 1880; Stirling: *Arbeiten aus der physiologischen Anstalt in Leipzig*, 1874.

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Whether, however, the delay in the response is due to the failure of the cytoplasm of the receiving cell to discharge until repeated impulses have reached it, or whether the modification of the cell which causes the delay is a process taking place at the point where the impulse passes over from the branches of one cell to those of another, is not directly determined by the experiments. The indirect evidence is, however, entirely in favor of the view that the delay which is notable in the arousal of a reflex response occurs at the point where the impulse passes from one cell to another.

C. The Nutrition of the Nerve-cell.

The metabolic processes within the nerve-cell are continuous, and the chemical changes there taking place involve not only those prerequisite to the enlargement of the cell during growth, but also those leading to the formation of such substances as by their breaking down release the energy that appears in the nerve-impulse. The passage of the nerve-impulses probably alters the osmotic powers of the cell-wall toward the surrounding plasma, and this of course is fundamental to the nutritive exchange. It follows, therefore, that the passage of nerve-impulses is one factor determining the nutrition of these cells.
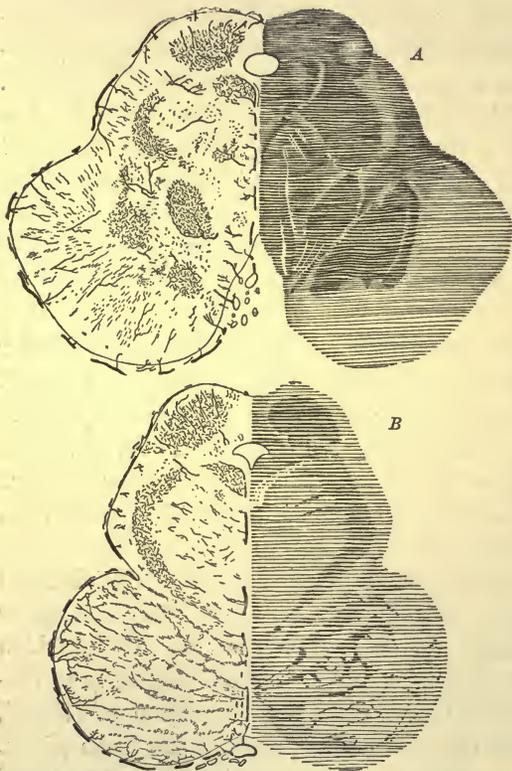
Fig. 155.—Frontal sections through the human mid-brain at *A*, level of the anterior quadrigeminum; *B*, level of the posterior quadrigeminum (Shimamura). On the left side the blood-vessels have been injected; on the right the gray matter is indicated by the heavy lines. It appears by this that the blood-vessels are most abundant in the gray matter.

Cell-body.—Histologically we look upon the cell-bodies as the part in which the most active changes occur, since the network of blood-vessels is most dense about these, indicating that the metabolic processes are here most active[1] (Fig. 155).

Chemical Changes.—For the direct micro-chemical determination of special substances within the nerve-cells there are but few methods, though some phosphorus-bearing substances (nucleins) can be demonstrated,[2] and the occurrence

[1] Shimamura: *Neurologische Centralblatt,* 1894, Bd. xiii.
[2] Lilienfeld und Monti: *Zeitschrift für physiologische Chemie,* 1892, Bd. xvii.

of chemical changes due to activity and to age are very evident. The nature of these latter changes is quite unknown. There is general consensus that the alkalinity of the nerve-tissues is decreased during activity, and this decrease in alkalinity may amount at times to a positively acid reaction.[1] This change, too, is better supported by the observations made where the cell-bodies are numerous, than by those made where the fibres are alone present.

Trophic Influences.—When a nerve-cell is not kept active by the passage of nerve-impulses through it, it usually atrophies and may degenerate. The reason for this appears to lie in the fact that the loss of those changes which accompany the nerve-impulses decreases the vigor of the nutritive exchange with the result of causing a steady diminution in the volume of the cell or even its disintegration. Such changes are found, for instance, in the nerves after the amputation of the limb to which they were supplied.[2]

The result of an amputation is that portions of the neurons originating from cell-bodies located either in the ventral horns of the spinal cord, or in the cells of the spinal ganglion, are removed. In the latter case the normal pathway for the incoming impulses is interrupted at its peripheral end, and in the former the last part of the pathway by which the impulse is delivered at the periphery is destroyed (see Fig. 156).
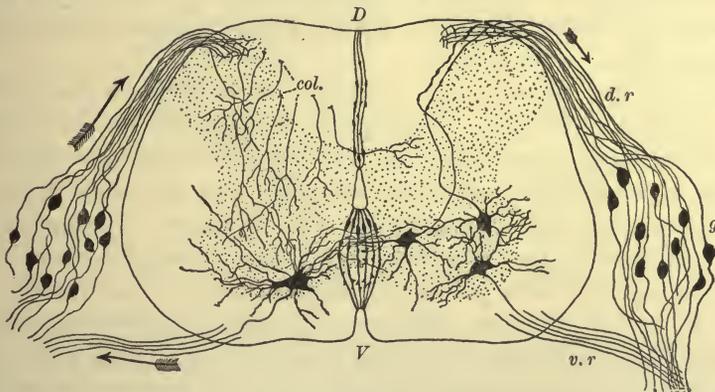
FIG. 156.—Cross section of the spinal cord of the chick, × 100 diameters (van Gehuchten): *D*, dorsal surface; *V*, ventral surface; *d.r*, dorsal root; *v.r*, ventral root; *g*, spinal ganglion. On the left the arrows indicate the direction of the larger number of impulses in the dorsal and ventral roots respectively. The small arrow on the right dorsal root calls attention to the fact that some neurons arising in the ventral plate emerge through the dorsal root and convey impulses in the direction indicated.

The disturbance caused in the two sets of cells is, however, not the same. In the case of the cells of the spinal ganglion the chief pathway by which they are stimulated under normal conditions, is so far mutilated that only a comparatively small number of impulses passes over them. That some do pass, is indicated by the sensations apparently coming from the lost limbs—sensations which are often very vivid and minutely localized.[3]

[1] Gscheidlen: *Archiv für die gesammte Physiologie*, 1874, Bd. viii.
[2] Grigoriew: *Zeitschrift für Heilkunde*, 1894, Bd. xv.
[3] Weir-Mitchell: *Injuries of Nerves*, Philadelphia, 1872.

On analyzing the condition thus established by an amputation it is seen that the cells located in the spinal cord are deprived by such an operation of one principal group of incoming impulses, namely those which arrive through the dorsal root-fibres that are most closely associated with them ; but at the same time there remain many other ways in which these same cells are normally stimulated. The efferent pathway from these cells is incomplete, and the impulses which must pass along the stumps are inefficient. That impulses do pass along the stumps of the efferent roots is beyond question, since, when the distal portion of an efferent nerve is cut off the cell can be shown to still discharge through the portion of the fibres connected with the cell-bodies. Moreover, the muscles of any stump tend to execute the associated contraction which they normally perform, thus showing that the group of cells is fully innervated, although its discharge is without mechanical significance, and finally there is always a tendency to the regeneration of the cut fibre which indicates activity through its entire length.

It is therefore not improbable that after amputation impulses do pass down even those fibres which end without physiological connections. It is explicable from this that in the case named the spinal ganglion cells should be more affected than those of the spinal cord. Further, since the efferent cells of the leg are more commonly innervated bilaterally than are those of the arm, we might expect the efferent cells in the cervical region to be more readily affected by an amputation.

Wherever in the central system a group of fibres forms the chief pathway for the impulses arriving at a given group of cells, then the destruction of these afferent fibres brings about the more or less complete atrophy of the cells with which they are secondarily associated, and this effect is the more marked the younger the animal at the time of injury. Examples of this relation are found in the " nuclei " of the sensory cranial nerves.

Thus the activity of a given cell has the value of contributing to the strength of its own nutritive processes, and different cell-elements, so far as they are physiologically united, stand in a nutritive or trophic relation to one another such that the cell receiving impulses is in some measure dependent for its nutrition on the cell which delivers the impulses to it.

Fatigue.—It is a familiar fact that living tissues may be fatigued. In the nervous system the signs of fatigue are both physiological and histological, but it is to the latter changes only that attention will be here directed.

Not only is the food-supply to the nerve-cells, as represented by the quality and quantity of the plasma, variable, but the cells themselves are subject to wide variations in their power to use the surrounding substances.

When in a nerve-trunk containing both afferent and efferent spinal root-fibres passing to a limb, the afferent fibres are stimulated by a faradic current applied intermittently, changes in the cell-bodies in the spinal ganglion are to be observed (Hodge).

When this experiment is made on a cat, and, after death, the sections from the stimulated are compared with those from the corresponding but

unstimulated spinal ganglion, a picture like that represented by Figure 157 is obtained.[1]

The sections indicate that the cytoplasm together with the enclosed nucleus and nucleolus as well as the nuclei of the enclosing capsule of the cell, have
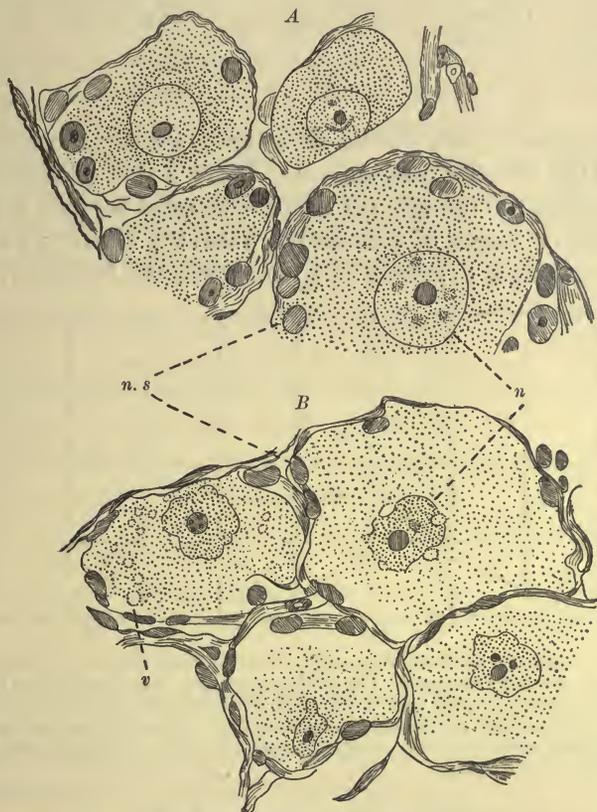
Fig. 157.—Two sections, *A* and *B*, from the first thoracic spinal ganglion of a cat. *B* is from the ganglion which had been electrically stimulated through its nerve for five hours. *A*, from the corresponding resting ganglion. The shrinkage of the structures connected with the stimulated cells is the most marked general change. *n*, nucleus; *n. s*, nucleus of the capsule; *v*, vacuole; × 500 diameters (Hodge).

all suffered change by this treatment. The stimulus was applied for only fifteen seconds of each minute, the remaining forty-five seconds being given to rest. In this way the cells here figured had been stimulated over a period of five hours. The nuclei of the sheath are flattened, the cytoplasm somewhat shrunken and vacuolated. With osmic acid the nuclei of the stimulated cells stain more darkly and the cytoplasm less darkly than in a resting cell. The nucleus is shrunken and crenated, and the nucleolus is also diminished in size.

In the first experiments the attempt was made to demonstrate a *measurable* change within the nerve cell-bodies as the result of stimulation. Assuming the nuclei of these cells to be approximately spherical, and calculating their volume as spheres, the shrinkage amounted to that shown in the following table:

[1] Hodge: *Journal of Morphology*, 1892.

Table showing the Decrease in the Volume of the Nucleus of Stimulated Spinal Ganglion-cells of Cats. Stimulation for fifteen seconds alternating with rest for forty-five seconds (Hodge).

Stimulation continued for—	Shrinkage in the volume of the nuclei of the stimulated cells.
1 hour	22 per cent.
2.5 hours	21 " "
5 "	24 " "
10 "	44 " "

This table further shows that the shrinkage is greater, the greater the time during which the stimulus was applied. There is thus established not only the fact of a change in the cell, but also a connection between the amount of this change and the length of time during which the stimulus was allowed to act. The results when expressed by a curve yield the following:
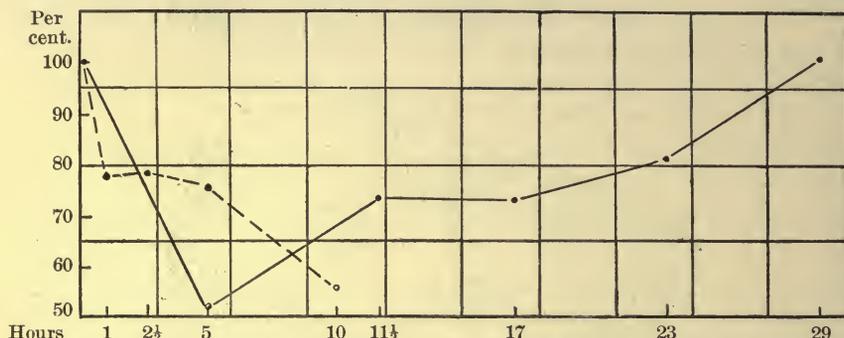
FIG. 158.—The broken line indicates the volume of the nuclei of the spinal ganglion-cells of a cat after stimulation for the times indicated. The solid line indicates the volume of the nuclei, first after severe stimulation for five hours, and then in other cats, also stimulated for five hours, but subsequently allowed to rest for different periods of time. The period of rest is found by subtracting five hours from the time at which the record is made. After twenty-four hours of rest the nucleus is seen to have regained its normal volume (Hodge).

Table to show Influence of Rest.

Right brachial plexus of each Cat stimulated in the same manner for five hours. Cat allowed to rest for a variable time after the stimulation had been stopped.

	Nuclei.				Cells.
	Rest.	Mean diameter of nuclei in μ.	Shrinkage.		Mean diameter in μ.
Cat, 17	0 hours.	16.40 Left, normal. / 12.93 Right, stimulated.	48.8%		57. / 52.
Cat, 16	6.5 hours.	16.70 Left, normal. / 15.09 Right, stimulated.	26%		56 / 54
Cat, 21	12 hours.	16.34 Left, normal. / 14.73 Right, stimulated.	26%		55 / 51
Cat, 19	18 hours.	17.08 Left, normal. / 16.03 Right, stimulated.	18%		56 / 55
Cat, 18	24 hours.	17.01 Left, normal. / 17.11 Right, stimulated.	+2%		
Cat, 7	Normal.	14.20 Left. / 14.54 Right.	+6.9%		

Whether these changes could be considered similar to the normal physi-

ological variations depended on whether it was possible to demonstrate recovery from them. This was accomplished in the following manner.

Under fixed conditions a cat was stimulated in the usual way and the amount of shrinkage in the nuclei of the spinal ganglion-cells was determined. This was found to be almost 50 per cent. Four other cats were similarly treated and then allowed various periods (six and a half, twelve, seventeen, and twenty-four hours) in which to recover. The results appear in Figure 158 and the table on page 630.

The effects of stimulation described were found not only in the nerve-cells of cats, but also in those of frogs which had been stimulated in a similar manner.

Having thus shown that the change was physiological in the sense that it was one from which the cells could recover, it remained to be shown that the features of the change were discernible in the living cell, and were not caused secondarily by the actions of the reagents employed in preparing the sections.

For the study of the living cell, frogs were chosen, and the cells of the sympathetic ganglia examined. In these experiments cells from different frogs were prepared under two different microscopes and kept alive in the same way by irrigation with a nutrient fluid. In one case, however, the cell was stimulated by electricity, while in the other no stimulation was applied. During the time of the experiment the cell which was not stimulated remained unchanged, while the stimulated cell went through the series of changes exhibited in Figure 159.[1]

So far as the main features are concerned the shrinkage and crenulation of the nucleus was essentially similar to that found in the nuclei of the spinal ganglion cells of cats. These results demonstrated therefore the natural character of those changes in the nerve-cells which had been found after treatment with histological reagents.

It followed that if these changes were really significant of normal processes they should be found in the nerve-cells of those animals which show well-marked periods of activity, alternating with periods of rest. To deter-

FIG. 159.—Showing the changes in the form of the nucleus resulting from the direct electrical stimulation of the living sympathetic nerve-cell of a frog. The hour of observation is given within each outline. The experiment lasted six hours and forty-nine minutes. A control cell treated during this time in the same manner, except that it was not stimulated, showed no changes (Hodge).

[1] Hodge: *Journal of Morphology*, 1892, vol. vii.

mine this, birds and bees were examined, one set of preparations being made from animals which were killed at the beginning of the day, after a night of rest, and the other from those killed at the end of the day, after a period of activity. Similar changes were found in the cells of the spinal ganglia of English sparrows, of the cerebrum of pigeons and cerebellum of swallows, and of the antennary lobes of bees (see Fig. 160).
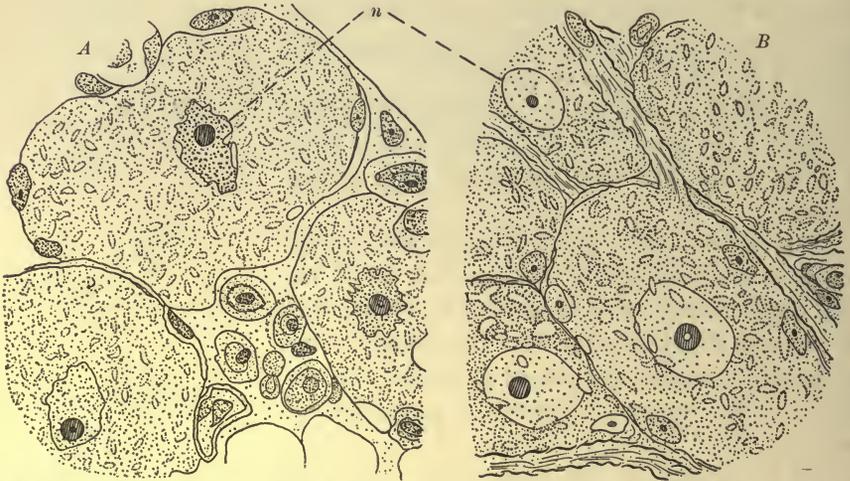
FIG. 160.—Spinal ganglion-cells from English sparrows, to show the daily variation in the appearance of the cells due to normal activity: *A*, appearance of cells at the end of an active day; *B*, appearance of cells in the morning after a night's rest. The cytoplasm is filled with clear lenticular masses which are much more evident in the rested cells than in those fatigued (Hodge).

A study of these figures shows the cells to be turgid with large round nuclei, at the beginning of the day after a night of rest, and on the other hand that they are vacuolated and shrunken and with altered nuclei at the end of an active period. These observations therefore justify the conclusions drawn from the appearances following direct stimulation.

Other observers [1] have obtained similar results. The motor cells of the spinal cord and cells of the retina (dogs, Mann) have been added to the list of those showing changes. After a short period of stimulation of the sympathetic cells of the rabbit, both Vas and Mann have found a preliminary swelling of the cell, and the same has been noted by Mann in the case of retinal cells in the dog.

The application of these observations to changes in the human nervous system has thus far been made only in a casual way, but enough has been already observed to make certain that the results are applicable.

It will be noted that the changes described follow variations in the amount of stimulation, the nutrient conditions represented by the surrounding plasma remaining nearly constant. This latter, however, may undergo alteration, and recent observations show that in various forms of poisoning by inorganic sub-

[1] Vas: *Archiv für mikroskopische Anatomie*, 1892; Mann: *Journal of Anatomy and Physiology*, 1894.

stances or in zymotic diseases, the nervous system and especially the cell-bodies are affected early and in a profound manner.[1]

With the establishment of these facts concerning the cell-body the question at once arises whether the nerve-fibres are in a like manner altered as a result of their activity.

The matter has been tested in this way : In a cat or dog a nerve-trunk was stimulated by a measured induction current, and the contraction of the muscle controlled by it, recorded. The physiological connection between the nerve and muscle was then interrupted by the giving of curare and the nerve was tetanized.[2] The stimulation of the nerve-trunk was continued in some cases for five hours. On the complete disappearance of the curare effects, a stimulus similar to that employed in the first instance was found to produce muscular contraction, thus showing that the continuous stimulation of the nerve-trunk during this interval had not seriously diminished its power to transmit the nerve impulses aroused in it.

Histological changes have also been sought for in the nerve-fibres after prolonged stimulation, but thus far they have not been demonstrated. Chemical changes in the nerve-fibres, if present, must be extremely small, and the thermal variations which occur amount to less than $0.0005°$ C., or, in other words, are not demonstrable.[3] Histological and chemical changes due to activity have therefore been seen in the cell-bodies alone.

Degeneration and Regeneration of Nerve-elements.—All parts of a nerve-cell are under the control of that portion of the cell-body which contains the nucleus; in this respect the nerve-tissues are similar to other tissues which have been studied, and in which the nucleated portion of the cell is found to be the more important. It was shown by Waller[4] that a nerve-fibre belonging to the peripheral nerves when separated from the cell of which it was an outgrowth soon degenerated from the point of section to its final distribution. The process is often designated as Wallerian degeneration. According to recent studies on this subject,[5] this degenerative change occurs practically simultaneously along the entire length of the portion cut off. The changes following the section consist in a fragmentation of the axis-cylinder followed by its disappearance, enlargement and multiplication of the nuclei of the medullary sheath, and absorption of the medullary substance, so that in the course of the fibres there is left at the completion of the process the primitive sheaths together with the sheath-nuclei. In the early stages of this process the medullary sheath, moreover, undergoes some changes, the result of which is that it stains more deeply with osmic acid, and hence appears very black in comparison with the normal fibres about it (Marchi).

Degeneration of Non-medullated Fibres.—Concerning the progress of

[1] Schaffer : *Ungarisches Archiv für Medicin*, 1893; Pandi: *Ibid.,* 1894; Popoff: *Virchow's Archiv*, 1894; Tschistowitsch : *Petersburger medicinische Wochenschrift*, 1895.

[2] Bowditch : *Archiv für Anatomie und Physiologie*, 1890.

[3] Stewart: *Journal of Physiology*, 1891, vol. xii.

[4] *Nouvelle méthode anatomique pour l'investigation du Système nerveux*, Bonn, 1851.

[5] Howell and Huber : *Journal of Physiology*, 1892, vol. xiii.

degenerative changes in the non-medullated fibres information is scanty. Bowditch and Warren[1] observed that when the sciatic nerve of the cat was sectioned, degeneration of the motor and vaso-constrictor fibres in the peripheral portion went on at about the same rate. Stimulation of the peripheral part of the nerve gave a vaso-dilator reaction after the vaso-constrictor reaction had entirely disappeared, suggesting that the constrictor fibres degenerate more rapidly than do the dilators, although it is not improbable that the dilator fibres in this location really belong to the medullated class (Howell). After five days no vaso-motor reaction at all could be obtained. In a recent study by Tuckett[2] of the degeneration of the non-medullated fibres contained in the branches springing from the superior cervical ganglion, it is stated that the degeneration as traced by histological and physiological methods is complete within thirty to forty hours after section of the fibres, and that the degenerative changes involve only the core of the fibres, the outside sheath and nuclei being unaffected.

Degeneration in the Central System.—In the central system, the distal portion of the fibres separated from the cell-body degenerate as at the periphery, and this reaction has therefore formed a means by which to study the architecture of the central system. The details of the process are, however, not well understood.

So far, then, as the principal outgrowth of the nerve-cell is concerned, it is found to be always under the nutritive control of the cell-body from which it springs. The changes which take place when the spinal roots are cut will serve to illustrate this control (see Fig. 161). Section of the dorsal root at the distal
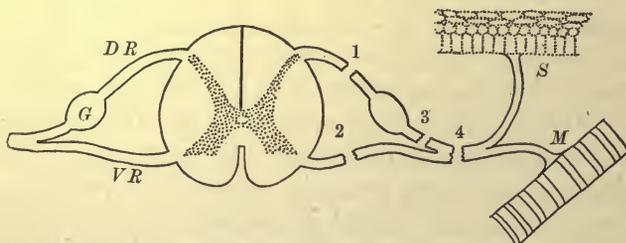
FIG. 161.—Schema of a cross section of the spinal cord, showing the dorsal and ventral roots and the points at which they may be interrupted: *D R*, dorsal root; *V R*, ventral root; *G*, ganglion; *M*, muscle; *S*, skin; 1, lesion between ganglion and cord; 2, lesion between muscles and cord; 3, lesion between skin and ganglion; 4, combination of 2 and 3.

side of the spinal ganglion at 3 causes a degeneration of all the fibres which form the dorsal nerve-root distal to the ganglion. Section of the dorsal root at 1 causes degeneration, central to the section, of those nerves which are outgrowths from the cell-bodies of the spinal ganglion. Section of the ventral root at 2 causes a degeneration distal to the point of section in those fibres which form the ventral root and which arise from the cells within the spinal cord. In each case, therefore, the degeneration occurs on one side only of the section, and that is the side away from the cell-body.

[1] *Journal of Physiology*, 1885, vol. vii.   [2] Tuckett: *Journal of Physiology*, 1896, vol. xix.

It is sometimes stated that degeneration takes place in the *direction* of the nerve-impulse. In a general way this is true, since the impulses usually travel from the cell-body along the neuron. In the case of the fibres arising from the cells of the spinal ganglion it is not true, since the section at the distal side of the ganglion causes degeneration away from the spinal cord, while that on the proximal side of the ganglion causes degeneration toward the spinal cord; yet in both neurons the impulse is in the same direction—namely, always *toward the cord.*

The distal portions of the nerve may be regenerated, or, under other conditions, the remainder of the neuron together with the cell-body from which it springs may atrophy, and this latter process may result in even the complete destruction of the nucleated portion.

Degeneration of Nucleated Portion.—In any case the internodal segment of the peripheral nerve-fibre which has been directly injured by the section degenerates centrally as far as the next node of Ranvier. Whether beyond this point any marked change is to occur depends on several circumstances. When regeneration is prevented, the younger the animals on which the operation has been made the more marked are the involutionary changes. These consist, first, in a stoppage of growth-processes in the elements affected; second, in a simple atrophy. Such, for example, are the changes taking place in the cells of the spinal cord after the amputation of a limb. Sometimes also true degeneration follows. That these effects may be very plain in man, the amputation should be one near the trunk—*i. e.* involving a great number of nerve-fibres, and be of long standing—*i. e.* more than one year.[1]

It was discovered by von Gudden[2] that when nerves in young animals are pulled away from their attachment with the central system, they most frequently break just at the point where they emerge from the cord or brain axis. When an efferent nerve is thus broken, in animals just born or very young, the remaining portion—*i. e.* the cell-bodies with so much of their neurons as lie within the central system—atrophies to complete disappearance. The cause of this complete disappearance in the case of very young animals thus injured, seems to lie in the intense struggle for nutriment among the nerve-elements themselves. Thus young cells meeting with injury are unable to compete with those about them for nourishment, and so perish. The bearing of such a fact is very direct. If in man there is reason to think that an injury was suffered during fetal life, there is a possibility that the injury may not only have prevented the further development of the cells involved, but may also have caused the complete destruction of some of them, in which case, of course, the architecture of the region is necessarily abnormal.

Such complete disappearance as the result of early injury has not been shown for cells which lie entirely within the central system, or for those forming the spinal ganglia. In the case of those central cells which form the sensory nuclei, like the sensory nucleus of the fifth nerve, or of the vagus,

[1] Grigoriew: *Zeitschrift für Heilkunde*, 1894, Bd. xv.
[2] *Archiv für Psychiatrie*, 1870, Bd. ii.

pulling out the nerve-trunk causes only an atrophy of the central cells, and not their complete disappearance.[1]

Regeneration.—When the two ends of the sectioned nerve are brought together under favorable conditions, the peripheral portion of the trunk may be regenerated. This occurs in the following steps as described by Howell and Huber.[2]

While the fragmentation and absorption of the myelin in the distal portion of the cut nerves is going on, the protoplasm in the neighborhood of the sheath-nuclei tends to increase. These enlarged masses of protoplasm then appear as a thread of substance within the old nerve-sheath. A new sheath is, however, soon formed on the protoplasmic thread, and the whole constitutes an "embryonic fibre." The embryonic fibres lying on one side of the cut unite with those on the other, union taking place in the intervening cicatricial tissue. Next the myelin appears in isolated drops, usually near the nuclei, and these subsequently unite to form a continuous tube, the formation of the myelin proceeding centrifugally from the wound. Then follows the outgrowth of the new axis-cylinder slightly behind the organization of the myelin into the tubular form.

It must not be forgotten that the last act, the formation of the axis-cylinder, is the important event, and while the whole process of repair may require many months, the rate at which the axis-cylinder, when started, grows out from the central end may be comparatively rapid. If this explanation be correct, namely that the axis-cylinder is an outgrowth from the central end, then the regeneration of the neuron is in so far but a repetition of the events by which it was originally formed. The development of the medullary sheath in its relation to the axis is, however, different in the two cases. When first regenerated, the fibres resemble normal young fibres in being small, but whether they later attain the size of those which they replace has not been shown. Moreover, it appears that the two functions of irritability and conductivity do not both return at the same time. The newly formed fibres are capable of conduction before they become sufficiently irritable to respond to artificial stimuli directly applied to them. In the first stages of irritability, also, the young fibres responded more readily to slight mechanical stimuli than to induction shocks—a differentiation in reaction which serves to suggest the complexity of the changes involved in the re-formation of the fibres.

Regeneration of this sort which is found in the peripheral system is not known to occur in the central system, although in many ways the conditions of such regeneration seem there most favorable. This fact also has its application in the use of the method of degeneration for determining architectural relationships; for when once caused to degenerate, the bundles of fibres thus altered can be tracked through the central system without fear that new growth-changes will obscure them.

The dorsal spinal root degenerates when the section is made between the

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[1] Forel: *Festschrift zur von Nägeli und von Kölliker*, Zürich, 1891.
[2] *Journal of Physiology*, 1892, vol. xiii.

cord and the spinal ganglion. Study of its development has shown that in the first instance the spinal ganglion becomes connected with the cord by the outgrowth from the cells of the ganglion of those fibres which form the dorsal root. It would follow that as the cells of the spinal ganglion can regenerate the fibres which pass toward the periphery, they should also be able to regenerate those which form the dorsal root, but as yet there have not been reported any cases where a dorsal root has been thus re-formed.

That the regeneration is due to an outgrowth of the central stump has been clearly shown by Huber,[1] who inserted a bone tube between the two ends of the sciatic nerve of the dog, and obtained regeneration of the nerve with a return of function although the initial interval between the two parts of the nerve was more than three centimeters. The rate of growth from the central end has been specially studied by Vanlair.[2] In the facial nerve of the rabbit, function was restored in eight months after section, and in the pneumogastric and ischiadic nerves of the dog in about eleven months. In the latter case, this gives an average rate of growth of about 1 millimeter a day. In the scar-tissue between the two parts of the nerve the rate is not more than 0.25 millimeter a day, and hence the return of function tends to be delayed by any increase in the distance between the cut ends of the nerve. It appears also that the return of the cutaneous sensibility is more rapid than the return of motion (Howell and Huber).

On testing the capacity of the sciatic nerve for repeated regeneration Vanlair found that in a dog, when it was cut a second time, it not only regenerated but did so more rapidly than in the first case.

Much interest has always attached to the exact course taken by the regenerating fibres. They appear in a general way to be guided by the old sheaths of the peripheral portion. But the peripheral nerves contain both afferent and efferent fibres, and it would appear most probable that in the process of re-formation these should undergo much rearrangement. Since the peripheral portion of the nerve acts as a guide to the growing fibres, the experiment has been tried of cross-suturing. Thus Howell and Huber[3] having cut both the median and ulnar nerves in dogs, sutured the central end of one nerve to the peripheral end of the other, and obtained reunion with extensive return of sensation and movement, and without inco-ordination to be attributed to the unusual arrangement of the nerve-fibres. Such a rearrangement without inco-ordination is not easy to explain in view of the association of certain functions, such as the control of a given set of muscles, with a special cell-group in the cord. The most remarkable observation, however, on the regeneration of nerve-trunks has recently been reported by Langley.[4] The pre-ganglionic nerve going to the superior cervical ganglion of the cat is composed of fibres with several functions. These fibres are derived from the first thoracic nerve, which mainly controls those cells in the ganglion that are

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[1] *Journal of Morphology*, 1895, vol. xi.

[2] *Archiv de Physiologie normale et pathologique*, 1894.

[3] *Loc. cit.*   [4] *Journal of Physiology*, 1895, vol. xviii.

connected with the pupil and the nictitating membrane; from the second thoracic nerve, which is mainly associated with the cells controlling the blood-vessels of the ear and in a less measure the nictitating membrane; from the third thoracic, which connects with a few cells which control the pupil; from the fourth thoracic, which connects mainly with cells controlling the erection of the hairs on the face and neck; from the fifth thoracic, which connects with the cells controlling the vessels of the ear, and also the hairs of the face and neck; and from the sixth and seventh thoracic, supplying hairs only. When the pre-ganglionic fibres were cut, therefore, and allowed to regenerate, various things might happen. The newly-formed fibres might grow past the ganglion, or they might form novel connections with the cells there contained, or finally, they might repeat the original connections. As a matter of fact, the last arrangement is the one accomplished, and in the case of the cat used in this experiment, stimulation of the nerve-roots above mentioned gave after regeneration the reactions characteristic for the several roots. It would appear, therefore, that in some way each group of the regenerating pre-ganglionic fibres had selected those cells which they had originally controlled.

The regeneration which has thus far been described has been that of the non-nucleated neuron by that portion of a nerve-cell which was nucleated. The regenerated portion always lies in the peripheral nervous system. Concerning the regeneration of the dendrons there are no observations.

The possibility of the formation of entirely new cell-elements in the process of repair remains to be mentioned. When the central system is injured it sometimes happens that mature nerve-cells there present show in their nuclei those changes which are characteristic of nuclei about to divide, but division does not take place[1] either in the nuclei or in the cell-bodies. In mammals there is no convincing record of the formation of new nerve-cells in the central nervous system of the mature animal. In some lower vertebrates (lizards) regeneration of the spinal cord has been reported, and in the newt such regeneration has been obtained in the retina, but the result in both cases appears to be due rather to the enlargement of embryonic cells still remaining in these regions than to an exhibition in the mature cells of powers absent from the corresponding cells of the mammalia. At various times and in several places the idea has been advanced that in the peripheral nervous system at least there was in progress a continuous process of degeneration and regeneration, as though this portion of the system was being continually renovated. What is known of the fixity of the central system and of the relation between the central system and that of the periphery, very strongly supports the idea that change in one would necessitate change in the other, and for central changes of this sort the evidence has never been advanced. To be sure, slow growth-changes occur in the central system until after the thirtieth year, but the additions which are thus made result from the enlargement of nerve-cells there present as structural units from a very early age, and such

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[1] Sanarelli: "I processi riparativi nel Cervello e nel Cervelletto," *R. Accademia dei Lincei*, 1891.

repair as is made occurs in the peripheral system only, while a cell once damaged by injury to its nucleated portion is not to be replaced.

PART II.—THE PHYSIOLOGY OF GROUPS OF NERVE-CELLS.

A. Organization and Architecture of the Central Nervous System.

The reactions of groups of associated nerve-cells have usually furnished the largest mass of facts presented under the title of the physiology of the central nervous system. When it was recognized that the nerves formed pathways by which the sensory surfaces of the body were put into connection with the central system, and also the pathways by which this system was in turn rendered capable of controlling the tissues of expression, it became at once important to determine over what nerves the impulses arrived at the central organ, how they travelled through that organ, and by what other nerves they were again delivered at the periphery.

Both anatomical and physiological research have been directed to this end.

The arrangement of these paths as found in the adult human nervous system is our principal object; at the same time it should not be forgotten that the reactions of simpler mammalian systems have furnished the greater number of facts, and if the pitfalls surrounding the assumption that the reactions found in the nervous system of a rabbit or monkey hold true in all detail for that of man can be avoided, no danger and much gain will follow from the use of the facts of comparative physiology.

Physiological Unity of the Central Nervous System.—So far as its physiology is concerned, the nervous system of any mammal must be regarded as a unit. Custom, however, sanctions a division into a central and peripheral nervous system. The central system is usually taken as that enclosed within the bony cavities of the cranium and vertebral canal, excluding the dorsal root-ganglia; the peripheral, that formed by the spinal and cranial nerves and the ganglia associated with them. Neither of these parts has an independent significance, and furthermore the central system is largely penetrated by nerve-fibres from the dorsal spinal roots, fibres which have an origin outside of those cells which form the walls of the medullary tube and constitute the central system in the strict morphological sense. On the other hand, the retina, which is in large measure morphologically a part of the medullary system, is, as a rule, not counted as belonging to this system, but is put down as a peripheral sense-organ. These facts are here mentioned solely to emphasize the point that gross anatomy has found convenient certain methods of division which, if strictly followed, confuse the morphological relations. Yet, for many purposes, the subdivision into central and peripheral portions is advantageous.

General Arrangement of the Central Nervous System.—The general architecture of the central system is best understood by means of schemas (Figs. 162 and 163). As the typical arrangement is found in the spinal cord, a cross section through this part will most readily express the facts.

The dorsal root-fibres among the spinal and cranial nerves, together with their homologues in the retina and the olfactory region, are the only channels for the entrance of impulses into the central system. Once having arrived there, the impulses cause other cells to discharge, and these in turn still others, through an indefinite series. The original impulse may thus arouse many other impulses within the system, and these spread until some of them reach cell-bodies which give rise to efferent fibres and which discharge away from the central system. The efferent fibres pass out mainly by the ventral roots, but in part by the lateral (when present) or by the dorsal roots (Fig. 163). Such efferent fibres end either directly in striated muscle tissue, or in the neighborhood
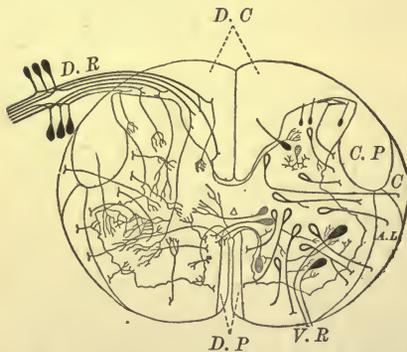
FIG. 162.—Schema of the arrangement of the human spinal cord as seen in cross section; for clearness the afferent fibres are shown on the left side only, efferent and central cells on the right side only (von Lenhossek): *D. R*, dorsal root; *V. R*, ventral root; *D. P*, direct pyramidal fibres; *C. P*, crossed pyramidal fibres; *C*, direct cerebellar tract; *A. L*, antero-lateral tract; *D. C*, dorsal columns. The various classes of cell-bodies are indicated by the manner of drawing.
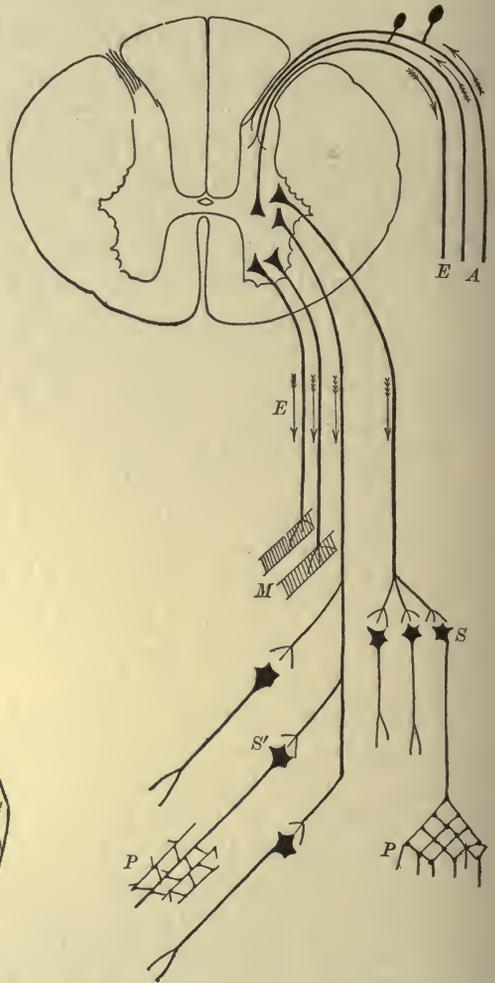
FIG. 163.—Schema of the distribution of the efferent fibres of the spinal roots. *A*, afferent fibres in the dorsal root only; *E, E*, efferent fibres in both dorsal and ventral roots. In the ventral root one group of efferent fibres goes to *M*, the striped muscles; another group to ganglion cells, *S*, forming a single sympathetic ganglion, or to *S'*, cells located in more than one sympathetic ganglion, but all connected with one efferent fibre by means of its collaterals; *P*, peripheral plexuses into which the neurons of some sympathetic cells run.

of ganglia (sympathetic ganglia). The fibres from the ganglia, in turn, very often connect with a peripheral plexus, such as the double plexus of Meissner and Auerbach, or the plexuses about the blood-vessels.

The evidence for the foregoing statements is briefly the following: The

experiments and observations of Sir Charles Bell (1811) and Majendie (1822) showed that sensation followed the stimulation of the central ends only of the dorsal nerve-roots, and that direct contractions of the skeletal muscles occurred only when the peripheral portions of the ventral and lateral roots were stimulated.

It had previously been shown by Hales and Whytt (1768) that even though both roots were intact, destruction of the spinal cord prevented the excitation of the dorsal roots from causing a reflex response, and hence the cord was to be regarded as forming part of the pathway. Moreover, it had been shown by the earlier investigators, before Bell, that the excitation of the ventral roots produced a response. Brown-Séquard[1] showed that section of the (last six thoracic and first two lumbar) dorsal roots caused (in guinea-pig, rabbit, and dog) a vascular dilatation and a rise of 1° to 3° C. in the hind limbs. Stricker showed that stimulation of the peripheral ends of the cut dorsal nerves caused a rise in the temperature of the foot; and Morat showed that stimulation of the peripheral end of a cut dorsal root produced vaso-dilatation. The studies in the degeneration of the nerve-fibres[2] show a small group in the dorsal root which, upon section of the root between the ganglion and cord, degenerates toward the periphery and remains intact toward the cord—a behavior which is precisely opposite to that which occurs in the case of the fibres taking origin from the spinal ganglion-cells.

Finally, van Gehuchten and others have shown, that in histological preparations (chick), these fibres can be traced through the ganglion itself (see Fig. 163). In the dorsal roots of the lumbar region of the monkey, Sherrington[3] was unable to find any *efferent* fibres. The connection of some of the ventral roots with sympathetic ganglia was established by Budge (1851), and physiological as well as histological observations show that the further connection of these ganglion-cells with the elements which they ultimately control is in many instances by way of the peripheral plexuses.

Classification of Nerve-elements.—In accordance with this arrangement of the nervous system, the elements which compose it fall into three groups: (1) The *afferent* cells, those whose function it is to convey impulses due to external stimuli from the periphery, including the muscles and joints, to the central system. The expression " external stimuli " is in this case intended to include also such stimuli as act within the tissues of the body, for example, those acting on tendons and muscles, and affecting the afferent nerves which terminate in them. (2) The *central* cells, those the neurons of which never leave the central system, and the function of which is to distribute within this system the impulses which have there been received. (2) The *efferent* cells, or those the neurons of which pass outside of the central system, and which carry impulses to the periphery. In this last group, again, two minor divisions may be made, namely, (*a*) the efferent elements the cell-bodies of which lie

[1] *Gazette médicale de Paris*, 1856.

[2] Gad and Joseph: *Archiv für Anatomie und Physiologie*, 1889.

[3] *Journal of Physiology*, 1895, vol. xvii.

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within the central system, as is the case with those giving rise to the ventral roots; (*b*) those forming the peripheral ganglia entirely outside of the central system—the sympathetic ganglia and the more or less solitary cells which take part in the formation of the peripheral plexuses.

Relative Development of Different Parts.—The bulk of the three subdivisions which have been named is by no means equal. The central system is far more massive than the afferent and efferent, taken together, but the relation cannot be stated with any exactness, since the mass of the peripheral system is not definitely known. The afferent and efferent groups are, however, about equal in weight, so that the comparatively small mass of either of them, taken alone, is apparent. When in addition to this disproportion it is further recalled that in both the groups last named the number of cell-elements is small as compared with the number which compose the central system, the disproportion is still further emphasized. That the central or distributive division of the nervous system is thus the most important is indicated also by the fact that, in the vertebrate series, as the complexity of the entire nervous system increases, the proportional development of the group of central elements is most marked.

Moreover, if we take the areas of the cross sections of the various spinal and cranial nerve-trunks as a measure, it is found that the areas for the afferent are greater than those for the efferent elements, and that the area of afferent nerves increases from the cord toward the encephalon.

Organization.—During early fetal life all the cells are isolated from each other. Either they are without branches as in the earliest state, or the branches, although formed, have not come into such relations with the neighboring elements that nerve-impulses are able to pass by way of them. The series of changes by which the elements are put into the most perfect physiological connection which they will ultimately attain may be designated as *organization*.

This change is dependent on two structural conditions—(*a*) the number of the dendritic branches, and of the terminal and collateral branches of the neurons, and (*b*) the relations in which these dendrons and terminal and collateral branches stand to one another.

In the case of cells like those of the cortex, it is to be seen from the instructive figure of Cajal (see p. 612), that in the vertebrate series the cortical cells tend to possess more branches the higher the animal stands in the series, *i. e.* the more complicated and adaptable its reactions. Further, the same figure shows that in the development of the individual cells it passes from a condition in which it has few to that in which it has many branches. Certainly the disposition of the cell-substance in the form of branches increases the surface thus exposed, and, assuming that the nutrition of the cell takes place over this surface generally, they increase its nutritive capacity. There is, however, another and more important standpoint from which they may be regarded. Cajal has suggested that the dendrons are the pathways by which impulses enter the cells. If this is true, then the number of dendrons characteristic of any group of cells may be taken as an index of the

variety of incoming impulses to which they are subject. In the case of the afferent, central, and efferent groups of cells, the following can be stated: Unless the branch which passes toward the periphery from the cells of the spinal ganglia be considered as homologous with the dendrons—*because* it carries incoming impulses—these cells are without dendrons but possess two neurons. In either case they are subject to but one group of impulses—those, namely, which enter the cell over the peripheral neuron. The central neuron ramifies widely within the central system.

Among the central cells we have the greatest variety of arrangement, the dendrons being insignificant in certain cells of the dorsal horns of the gray matter, and abundant in the large pyramidal cells of the cortex; or again, the granules of the cerebellar cortex with few dendrons may be contrasted with the large cells of Purkinje having many—these being taken merely as examples.

Finally, the bodies of efferent calls are characteristically supplied with a large number of dendrons—again an arrangement which fits with the physiological demands, as they must react to many stimuli though they discharge but one way and with but one sort of effect.

Connections between Cells.—In determining the connection between cells, the fact that the neuron is the outgrowth of a cell-body and that each cell is an independent morphological unit forms the point of departure. Under these circumstances the question of the connection between cells takes the more explicit form of the question whether cell-branches become continuous by secondary union. In mammals, man included, there is no good histological evidence that such secondary union occurs in the central system. A close approximation of the parts of two nerve-cells is alone to be seen. The means by which the cells are brought close together are not always the same. If the branching of the neurons in the neighborhood of the dendrons of the large pyramidal cells is subject to the interpretation that the impulses act across the small intervals that separate these two structures, then, when it is found that the neurons in some cases end in an enclosing basket or frame about the bodies of the cells of Purkinje, it would be correct to infer that the action took place between the terminals of the neuron and the *body* of the cell which they surround. If this infer-

Fig. 164.—Showing at the lower edge of the figure a series of basket-like terminations of neurons which surround the bodies of the great cells of Purkinje in the cortex of the cerebellum (Ramón y Cajal): *C*, cell-body; *N*, neurons; *B*, basket-like terminations arising from cell *C*, and enclosing the cells of Purkinje.

ence is correct, then the dendrons are not necessarily the sole pathways for the impulses which affect a given cell (see Fig. 164).

Theories of the Passage of the Nerve-impulse.—Accepting the view that the nervous system is composed of discontinuous but closely approximated cell-elements, it remains to explain how impulses arising within the limits of one element are able to influence others.

As an hypothesis, this may be assumed as dependent on chemical changes set up at the tips of the terminals and affecting the surrounding substance, which, thus affected, acts to stimulate the neighboring dendrons. As this is only an hypothesis, it may be left with the statement that it seems to fit in large measure the group of facts which it is necessary to explain.

The structural changes which permit the stimulation of one element to affect another are completed slowly, and, as we shall later see, these changes continue in some parts of the human nervous system up to middle life.

From what has just been stated it follows that the nervous system of the immature person is quite a different thing from that of one mature, since in the former it is more schematic, more simple, the details of the pathways not having been as yet filled out. Moreover, considering the slow and minute manner in which the central system is organized by the growth of the cell-branches, it is the last place where there should be expected structural uniformity in the details of arrangement.

B. The Physiological Anatomy of the Nervous System.

It follows from what has already been stated concerning the relations of cell-elements, that the impulse which enters the central system along a given dorsal neuron is bound to be first delivered to those cells in the neighborhood of which the branches of the neuron terminate.

Therefore, in determining the course that the impulses take, the determination of the mode in which the dorsal root-fibres are distributed is the first step.
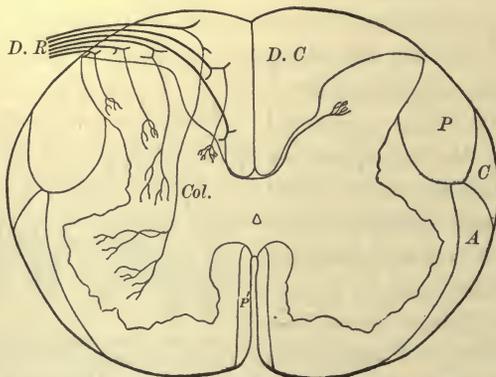
Fig. 165.—Schema of the human spinal cord: *D. R*, dorsal root, right side; *Col*, collaterals from the dorsal root-fibres; *D. C*, dorsal columns; *P*, crossed pyramid; *P'*, direct pyramid; *C*, direct cerebellar tract; *A*, antero-lateral tract.

Afferent Roots.—The manner of this termination is shown in Figures 151 and 165.

Here the afferent neuron having entered into the cord is seen to divide, and

send one branch caudad, while the other passes cephalad (Fig. 151). The length of these branches is difficult of determination, but it appears that the one passing cephalad is probably the longer as a rule, and that it may extend over nearly the entire length of the cord. By means of collaterals, these main branches are connected with cells within the cord, probably both efferent and central. Through the central cells arranged in series, pathways are formed by which the incoming impulses may produce an effect at parts of the system remote from the point of entrance, as well as pass almost directly to the efferent cells in the neighborhood where they enter.

Of these afferent roots there are thirty-one on either side, and for each dorsal root there is a corresponding ventral one. Due allowance being made for components which have failed to develop, the cranial nerves can be homologized with them. Considering, then, the longitudinal extension of the cord, it falls into a series of segments marked on each side by a pair of spinal nerves.

Segmentation.—The segmentation thus indicated is most evidently marked by the arrangement of the efferent or ventral spinal nerves. The studies on the relations between the efferent nerve-fibres and the cell-bodies which give origin to them indicate that the latter are located at the same level in the cord as that at which the fibres springing from them emerge. This permits us to infer that the cells of origin for any ventral root tend to concentrate in the segment from which that root springs.

The afferent nerve-fibres have in part at least a somewhat extended course through the cord, and are less strictly limited to the segment with which they make their superficial connections. At the same time, a number of central cells belong to each segment, and must be more closely connected with the dorsal and ventral nerves with which they are immediately associated, than with any others. Nevertheless the human spinal cord shows but poorly the segmental disposition of the elements in it when compared with that of lower vertebrates, like the snakes for example, in which the concentration of the nerve-cells about the region of emergence of the roots is more evident.

Bilateral Symmetry.—The body being in the main bilaterally symmetrical, it is to be expected that the nervous system which controls it will be constructed in the same manner. Such is, indeed, the case. Architecturally this symmetry is not perfect, since each cell on one side is not exactly balanced by a corresponding cell on the opposite side, but the number of cells in corresponding regions is approximately the same, and for physiological purposes the bilateral symmetry is quite complete. Yet this arrangement is not without exception.

Dorsal and Ventral Plates.—In the human fetus the shape of the medullary tube,—the tube from which, later, the brain and spinal cord are developed—is shown in cross section in Figure 166.

Slight indentations on either side of the tube are here evident on the inner wall. They divide each side of the tube into a dorsal and ventral portion,

and His[1] has followed these two portions, with a groove dividing them, through the entire length of the tube. The dorsal plate (*d. p.*) he designates as the *Flügelplatte* (literally, wing-plate), and the ventral plate (*v. p.*) as the *Grundplatte* (literally, foundation-plate). The interest attaching to these sub-divisions resides in the fact that the parts of the tube thus marked off are loci for cells having well-marked and different physiological functions. The incoming neurons arriving from the cells of the spinal ganglia are limited in the distribution of the main branches to the dorsal plate, and the cell-bodies which give rise to the efferent fibres are to be found in the ventral plate only. The central cells are present in both plates, though grouped in the locality where the two plates come together, and being rather more abundant in the dorsal one. The *collaterals* of the afferent fibres are distributed to both plates. There is thus in the cord a general arrangement whereby the central cells are located between the afferent neuron and the efferent cell-bodies. Far more important than this, however, is the relation which becomes evident as we pass cephalad—namely, that the cerebellum, quadrigemina, and almost the entire mass of the basal ganglia, together with the hemispheres, are the homologues of the dorsal plates, and contain central cells only (Fig. 167).
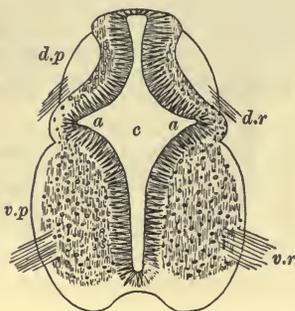
Fig. 166.—Cross section in the cervical region of a fetal human spinal cord at the sixth week; × 50 diameters (Kölliker): *c*, central canal; *a, a*, groove separating the two plates; *d.p*, dorsal plate; *v.p*, ventral plate, in which alone are located nerve-cells the neurons of which leave the central system; *d.r*, dorsal root; *v.r*, ventral root.
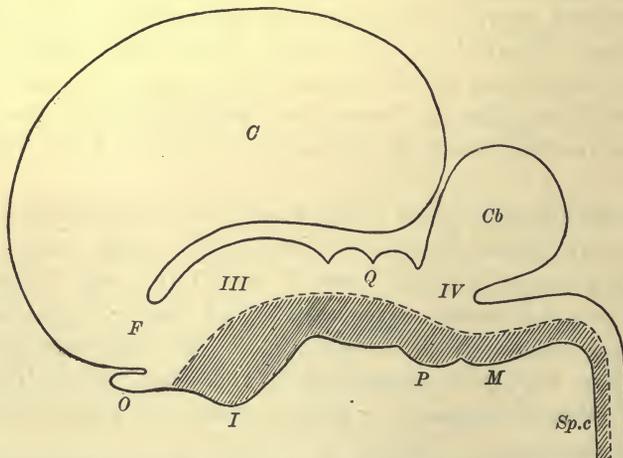
Fig. 167.—Schema showing the encephalon and cord; the unshaded portion is that derived from the dorsal plate; the shaded that from the ventral (from Minot): *C*, cerebrum; *Cb*, cerebellum; *F*, foramen of Monro; *I*, infundibulum; *M*, bulb; *O*, olfactory lobe; *P*, pons; *Q*, quadrigemina; *Sp.c*, spinal cord; *III*, third ventricle; *IV*, fourth ventricle.

[1] His: *Abhandlungen d. math.-phys. Classe d. königl. Sächs. Gesellschaft der Wissenschaften,* 1889.

There are then to be expected from these cells, forming as they do the great bulk of the central system, reactions of the same order as those occurring among the central cells of the cord.

Decussation.—All through the central system neurons pass from one lateral half to the other, witness for example the arrangements of the optic chiasma, the callosum, the decussation of the pyramidal fibres and the ventral commissure in the cord itself. It is to be noted, however, that the bulk of the commissures is small as compared with the masses which they connect. So far as known, the neurons of the dorsal roots that have entered the dorsal column of the cord on one side of the middle line do not cross, by their main stems at least, to the other side. As regards the efferent cells, it appears that the neurons of some of these do cross in the ventral commissure, but in the instances above given, and in the case of the greater number of fibres belonging to the ventral commissure, the neurons concerned are the outgrowths of central cells (Fig. 168). In the case of the central cells the decussation may be effected by the entire neuron or by a principal branch from it. Such is the arrangement in the case of certain cortical cells which send one branch to the callosum (Cajal). Besides these connections between parts lying symmetrically on either side of the middle line, there are of course dorso-ventral connections, but the neurons by which this is effected do not run in bundles and are therefore less obvious and probably less important.
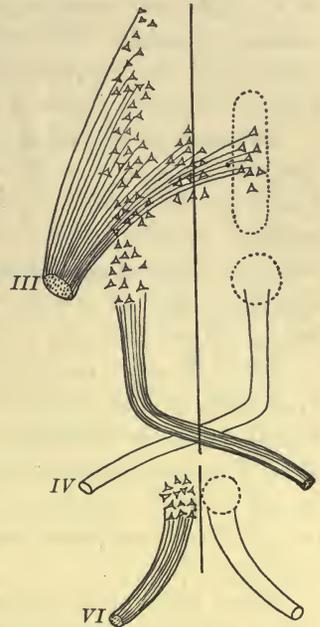
Fig. 168.—Illustrating the partial and complete decussation of the fibres of the third and fourth cranial nerves, and the absence of decussation in the case of the sixth: *III*, root of the third cranial nerve; *IV*, of the fourth; *VI*, of the sixth.

C. Pathway of the Impulses.

Conditions of Stimulation.—In speaking of the nerve-impulses we regard them as always initially aroused at the periphery, using this last term in a wide sense. The conditions necessary for this arousal are an external stimulus, acting on an irritable nerve-end. While life exists, stimulation of varying intensity is always going on, and hence there is no moment at which the nervous system is not stimulated and no moment at which the effectiveness of this stimulus is not varied. The response to this continuous and ever-varying stimulation is not necessarily observable, but occasionally the variation in the stimuli is so wide that an evident reaction follows.

Though the foregoing statements suggest that the chief variable is that represented by the stimulus, the strength of which changes, yet as a matter of

fact the variations in the physiological (chemical) condition of the nerve-cells are equally important, and neither factor can be studied independently.

The term central stimulation is sometimes employed. For example, the spasmodic movements of the young child, when there is no change noticeable in the external stimuli acting upon it, are sometimes attributed to this cause; but these, although doubtless due to central changes, altering the irritability of the cells, are most properly classed with the reactions which follow the external stimulus. The misconceptions here to be avoided are those of supposing that the nervous system is at any time unstimulated, and that the evident responses follow a change of the external stimulus only.

Strength of Stimulus and Strength of Response.—Where the impulse does not traverse more than *one* nerve-element, there is a direct relation between the strength of the stimulus and the strength of the response. The negative variation in the isolated nerve increases with the intensity of the stimulus which is sent through it. The same is true for submaximal stimuli applied to the nerve when the nerve is still attached to a muscle, and the height of the muscular contraction is measured.

When, however, the impulse in one cell-element is used to arouse an impulse in another, as in all experiments where the nerve-cells are arranged in a physiological series, the strength of the impulse from the second is less easy to predict. This is explained as due to variations in the ease with which the impulse in one element stimulates the next, and also to the variations in the second cell of those conditions which determine the intensity with which it may discharge.

When an impulse has once entered the central system the arrangement of the pathways involves the distribution of it to a larger and larger number of elements. This may be illustrated by Figure 169.

At the same time that the impulse is thus distributed it tends to die out. If, as we assume, it is a wave of molecular change that passes along the neuron, then when the neuron divides the energy in the main stem is distributed to the mass of substance which forms the branches, and if the mass of these, as is usually the case, is greater than that of the main stem, then the energy in any branch will be less than in the main stem.

In the case of some of the cells about which the branches of the neuron end the impulse will not be adequate to cause in them a discharge, although it may still produce a certain amount of chemical change in them. The impulse thus tends to disappear within the system, by producing in part chemical changes strong enough to cause a discharge, and in part similar changes of a less intensity.

Diffusion of Central Impulses.—Thus the general result of sending an impulse into the central system is that it tends to be distributed and at the same time to become weaker. Finally, by one or more of the central paths it reaches an efferent cell which is in a condition to discharge so as to produce an evident reaction.

If the previous description has been correct, two very important events

occur: in the first place, the impulse reaches a far greater number of cells than evidently discharge, and in the second, the pathway followed by the im-
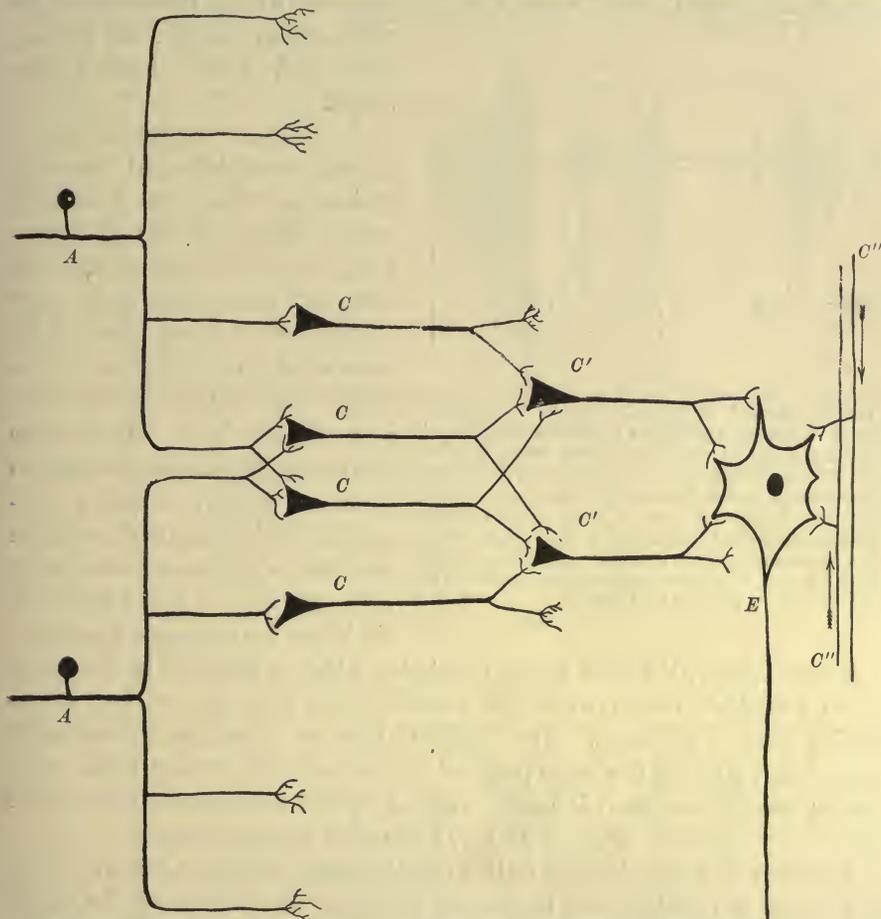
FIG. 169.—Schema to show how, by means of the collaterals and the central cells, several paths are open to any impulse coming in over *A,A*, also showing how an impulse may arrive at a given part of an efferent cell by more than one pathway among the central cells: *C,C, C′C′. C″C″*, neurons of central cells the bodies of which are located in other segments; *E*, efferent cell.

pulses which do produce the discharge is by no means the only pathway over which the impulses can or do travel.

The most convenient illustration of this process of diffusion can be obtained by a study of the knee-kick or knee-jerk as it is more commonly called. The reaction in question consists in a contraction of extensor muscles of the knee in consequence of a blow on the tendon just below the knee-pan. As a result of this contraction, the leg is extended, and a kick of greater or less extent is made from the knee joint. Very careful studies of the conditions controlling this response have been made by a number of investigators, notably Westphal,[1] Lombard,[2] Bowditch and Warren,[3] Weir-Mitchell,[4]

[1] *Archiv für Psychiatrie*, 1875. [2] *American Journal of Psychology*, 1887.
[3] *Journal of Physiology*, 1890. [4] *Philadelphia Medical News*, Feb., 1886.

Noyes.[1] It is found that under given conditions, the variations in the extent of the kick can be referred to variations in the excitability of that portion of the spinal cord from which the fibres controlling the muscles take their origin, namely, the second, third, and fourth lumbar segments.

In the same individual under constant conditions and for short periods of time, the knee-kick may be fairly constant in its extent, but the normal extent for different individuals may vary widely, all the way from those cases in which this reaction is normally absent to those in which it is normally very large. In the same individual there are also variations from day to day, variations comparable for instance to those in the condition of athletes whose capacity for performing a given feat is, as we know, by no means constant.

FIG. 170.—Record of the knee-kick of a demented patient. The knee was tapped at regular intervals of five seconds. While the patient was asleep and all about was quiet, no response was obtained; after such an irresponsive period the sound of some one walking on the floor below caused at *A* a series of kicks which gradually diminished; the same at *B*. At *C* two taps with a pencil and a distant locomotive-whistle produced a longer series. The arrow indicates the direction in which the record is to be read (Noyes).

Experimentally the most marked variation which is observed in the extent of the knee-kick occurs when the patient passes from the waking to the sleeping state, or *vice versa*. The regulated blow of a hammer automatically released, and striking the same point of the tendon, will produce little or no reaction when the patient is asleep, whereas in full wakefulness the reaction may be very evident. Figures 170, 171 illustrate such variations.

Attention was first directed to this peculiar reaction for the reason that in some degree it could be used to test the physiological condition of the spinal cord, it being found that the knee-kick was usually abolished in those conditions in which the lumbar portion of the cord is damaged or its connections with the higher centres interrupted, whereas it was much exaggerated in those conditions in which disturbance in the higher centres tended to cause excessive stimulation of the cord. As soon, however, as the reaction was studied with greater care in normal persons, it became evident that the condition of this part of the spinal cord was subject to remarkable fluctuations, and that these fluctuations depended in a measure on circumstances which could be controlled. For example, there are here given (Fig. 171) six records showing respectively the increase in the extent of the knee-kick after the subject was suddenly awakened; on repeating Browning's Poem, " How they brought the good news from Ghent to Aix; " as the result of talking; in consequence of the crying of a child in the next room; and immediately after swallowing. The point here insisted upon and for which illustration is sought by the accom-

[1] *American Journal of Psychology,* 1892.

panying figures, is simply this : that an extra stimulus caused by the condi-
tions just enumerated and sent into the central system, often at one very def-
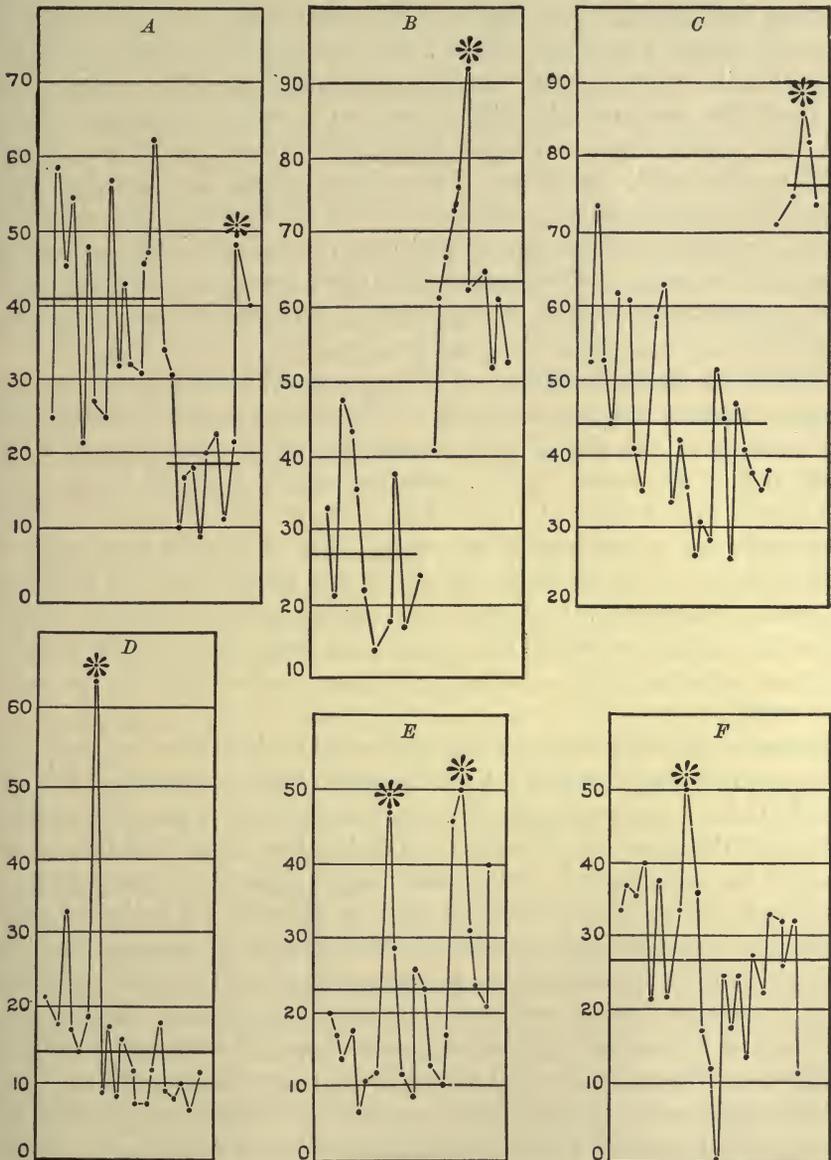
FIG. 171.—A series of small figures showing various reinforcements of the knee-kick (Lombard); curves
constructed from the original records. Numbers at the left indicate the height of kick in millimeters: *A*,
subject asleep, when the curve is lowest; * reinforcement after being called; *B*, first part of curve low;
* reinforcement in the knee-kick on repeating Browning's poem, "How they brought the good news from
Ghent to Aix." *C*, * reinforcement as the result of talking; *D*, * reinforcement due to itching of the ear;
E, * reinforcement due to the crying of a child in the next room; *F*, * reinforcement due to swallowing.

inite point, does not limit its influence to that immediate portion of the system,
but in all these cases the nerve-cells located in that portion of the spinal

cord which controls the knee-kick are so modified that the extent of the kick is noticeably altered.

There is little doubt that if there were a means of measuring other motor reactions and testing their variability as determined by variations in the incoming stimuli, results concordant with these just given could be obtained. They illustrate a fundamental condition in the reactions of the central system —namely, that every stimulus which falls upon it alters its responsiveness, and that it is continually in a state of tension due to the effect of many stimuli which we often fail to recognize. If we follow strictly the anatomical interpretation, it appears, as a consequence of these observations, that any nerve-impulse arriving over the afferent pathways can and does affect to a varying degree all the efferent cell-elements, that there must be a pathway for the nerve-impulses from some of the terminals of each afferent fibre to the neighborhood of each cell giving rise to efferent impulses.

Variations in Diffusibility.—The degree to which any set of incoming impulses modifies the responsiveness of the central system depends in the first instance on the physiological connections of the fibres by which they travel, and in the second, on the particular condition in which the central cells happen to be found. As to the first point, we should expect the afferent nerves with the widest central connections, such as the olfactory, optic, and auditory nerves, to be the most efficient in this respect, and this is the case. Concerning the second, it is observed, for example, that by means of drugs it is possible to alter the diffusibility of incoming stimuli to an enormous extent. Strychnin and drugs with a similar physiological action have this as one of their effects.

Influence of Strychnin.—The experimental study of strychnin-poisoning shows the following relations: A frog poisoned by the injection of this drug is easily thrown into tetanus whether the brain is intact or has been removed previous to the injection. The drug is found to have accumulated in the substance of the spinal cord.[1] The peculiar change wrought in the nervous system is such that a slight stimulus will cause an extended and prolonged tetanic contraction of the skeletal muscles, *i. e.* the diffusion of impulses within the cord is very wide and efficient to an unusual degree. The direct application of strychnin to the spinal cord has been carefully studied by Houghton and Muirhead.[2] When the strychnin solution was applied locally to the brachial enlargement of the spinal cord of a brainless frog, a subsequent stimulation of the skin of the arms produced tetanic contractions of the arms, and later, after the poison had acted for a time, of the entire trunk and legs. On the other hand, stimulation of the legs in such a case produced a slight reflex or none at all. Since in order to cause contraction of the leg muscles the efferent cells controlling the muscles of the leg must be discharged—and in the one case when the stimulus was applied to the arm region these cells discharged so as to cause a tetanic spasm, while in the other, when the stimulus was applied to the legs, they discharged only slightly—the alteration in the cord produced by

[1] Lovett: *Journal of Physiology*, 1888, vol. ix.   [2] *The Medical News*, June 1, 1895.

the drug must affect some other group than these efferent cells. Since, moreover, a tetanus of the legs could be caused by the stimulation of the skin of the arm, the application of the drug being to the brachial enlargement only, it appears that the central cells, or those conducting the impulses entering by the dorsal root-fibres in the brachial region to the nuclei of the lumbar enlargement, are probably affected; and further, that it is the bodies of these cells on which the drug must act, since they alone were in the locality at which the drug was applied. The application of the drug to the dorsal root-ganglia and to the nerve-roots between the ganglia and the cord proved to be without effect, so that the two parts which can possibly be influenced are the terminations of the sensory afferent nerves within the cord and the bodies of the central cells with which these terminations are associated. But whether the change is in both these structures or only in one cannot now be determined.

The diffusion of impulses in the central system depends anatomically not only on the amount of branching among the neurons of the individual central cells, but also on the association of many cells together so as to accomplish this wide distribution of the impulses. In the case of the afferent elements, as we have seen, the diffusion depends on the branching of the neurons alone.

Peripheral Diffusion.—Turning next to the efferent system, we find the conditions for diffusion dependent on the arrangement of several cells in series. When a group of efferent cells discharges, we know from the arrangement of the ventral roots that the impulses leave the cord mainly along the fibres which comprise these roots, but where the lateral root is present they may also pass out over it, as well as over the few efferent fibres found in the dorsal roots. These neurons carrying the outgoing impulses have two destinations: (1) The voluntary or striped muscle-fibres; (2) the sympathetic nerve-cells, grouped in masses to form the vagrant ganglia (see Fig. 163).

In the case of those neurons passing to the voluntary muscles, the impulses are distributed to the muscle-fibres to which the final branches of the neuron extend, but there is no evidence that in these localities the impulses, having entered a given muscle-cell, necessarily pass beyond the limits of that cell by conduction through the muscle-substance. It thus happens that one part of a large muscle can be innervated by one bundle of fibres and another part by a different bundle, or that the same parts of a muscle may be innervated by fibres which reach it through more than one ventral nerve-root, and also that with a given stimulus the strength with which a muscle contracts depends on the proportion of the neurons stimulated, and therefore on the proportion of the muscle-fibres thrown into contraction.[1]

When the impulses are thus sent out there is in the case of motor nerves no diffusion, the effect being limited to the peripheral distribution of the efferent nerve-elements by way of which the impulses leave the central system. The fibres going to the voluntary muscles form, however, but one portion, which

[1] Gad: "Ueber einige Beziehungen zwischen Nerv, Muskel, und Centrum," *Würzburger Festschrift*, 1882.

has just been indicated as group 1. The connections of the remaining group (2) are still to be examined.

Sympathetic System.—Associated with the efferent neurons of the cerebro-spinal system, and with these alone, is the series of vagrant ganglia and also of peripheral plexuses containing ganglion-cells, which taken together form the sympathetic system.[1] This system is composed of nerve-cells always mononeuric but sometimes with and sometimes without well-marked dendrons. The cells are more or less grouped in ganglia, and these ganglia interpolated between the efferent neurons of the spinal nerve-roots on the one hand and the peripheral plexuses or secreting cells on the other. The number of cells in the ganglia is greater than the number of spinal neurons going to them, and hence their interpolation in the course of the ventral fibres increases the number of pathways toward the periphery, as is shown in Figure 163. In speaking of the fibres concerned it is desirable to distinguish between the pre-ganglionic, or those originating in the medullary centres and passing to the ganglia, and the post-ganglionic fibres, or those originating in the cells of the ganglia and passing to the periphery.

Following the histological observations of Gaskell[1] and the physiological studies of Langley,[2] previously quoted, an outline of the relations of the sympathetic cells, based on those found in the cat, is briefly as follows:

Pre-ganglionic fibres, *i. e.* those growing out of cell-bodies located in the cord, arise from the first thoracic to the fourth or fifth lumbar, and from these segments only (Gaskell). The fibres are medullated. Langley's experiments indicate that no sympathetic cell sends a branch to any other sympathetic cell. It has been shown that the pre-ganglionic fibres are interrupted in the ganglia. The post-ganglionic fibres are in part medullated, though sometimes medullation occurs only at intervals, but in the main they are gray or unmedullated.

The cerebro-spinal neurons end in the ganglia in such a manner that the branches of the pre-ganglionic neuron are distributed to a number of the ganglion cell-bodies, and these cells in turn send their neurons either directly to the peripheral structures controlled by the sympathetic elements or to the plexuses such as are found in the intestine and about the blood-vessels.

The same pre-ganglionic fibre may have connections with several cells in one ganglion, or, by means of collaterals, connect with one or more cells in a series of ganglia (Langley).

Manner of Diffusion.—It has been found that while the cells in a sympathetic ganglion are so arranged that one pre-ganglionic fibre may be in connection with a group of cells, and thus the impulses which pass out of the ganglion be more numerous than those which entered it, yet the several *groups* of cells within the ganglion are not connected. In the peripheral plexuses there appears to be a different arrangement.[3]

[1] Gaskell: *Journal of Physiology*, 1885, vol. vii.; von Kölliker: "Ueber die feinere Anatomie und die physiologische Bedeutung des sympathischen Nervensystems," *Verhandlungen Gesellschaft deutscher Naturforscher und Aerzte*, 194, Allgemeiner Theil, 1894.

[2] Langley: "A Short Account of the Sympathetic System," *Physiological Congress*, Berne, 1895.

[3] Berkeley: *Anatomischer Anzeiger*, 1892.

It has been observed upon stimulation of the branches of the cœliac plexus in the dog, that the several branches, though unlike in size, bring about nearly the same quantitative reaction, in the constriction of the veins, from which we infer that though entering the peripheral plexus by different channels, the impulses find their way to the same elements at the end, owing to a multiplicity of pathways within the plexus.[1]

Experiments with strychnin on the more proximal sympathetic ganglia do not show any increased diffusibility following the application of the drug, but on the other hand, Langley and Dickinson[2] have shown that nicotin applied to various sympathetic ganglia of the cat produces a condition whereby electrical stimulation below the ganglion, which in the normal animal is followed by dilatation of the pupil, is without effect. Since the application of the drug to the nerve-fibres on either side of the ganglion is ineffective, when at the same time the application to the ganglion itself is effective, it is inferred that the drug acts by altering some peculiar relation existing within the ganglion, and the relation which is assumed to be thus modified is that between the fibres terminating in the ganglion and the cells which they there control. The relation between the post-ganglionic fibres and the peripheral plexuses is not interrupted by nicotin, and hence is different from that between the pre-ganglionic fibres and the cell-bodies which they control.

Evidence for Continuous Outgoing Impulses.—Under normal conditions, striped and unstriped muscular tissues are always in a condition of slight contraction. When the nerves controlling any such set of muscles are cut, or their central connections injured, the muscles at first relax.

If a frog, rendered reflex by the removal of the brain, the cord remaining intact, be hung up vertically, it is found that the legs are slightly flexed at the hip and knee. If now the sciatic nerve be cut upon one side, the leg on the side of the section hangs the straighter, indicating that the muscles have relaxed a little as the result of the section of the nerve; if, in the same animal, the smaller arteries in the web of the foot be examined both before and after the section, it is found that after the section they have increased in diameter. Conversely, artificial stimulation of the peripheral stump causes a contraction of the vessels, but it is not possible in so rough a way to imitate the tonic contraction of the skeletal muscles.

It is inferred from these experiments that normally there pass from the central system along some of the nerve-fibres impulses which tend to keep the muscles in a state of slight contraction. Destruction of the entire cord abolishes all outgoing impulses, and produces a complete relaxation of these muscles.

Though the intensity of these outgoing impulses is normally always small, yet it is subject to significant variations. The difference between the tone of the muscles of an athlete in prime condition and those of a patient recovering from a prolonged and exhausting illness is easily recognized, and this difference is in a large measure due to the difference in the intensity of the impulses

[1] Mall: *Archiv für Anatomie und Physiologie*, 1892.
[2] *Proceedings of the Royal Society*, 1889, vol. xlvi.

passing out of the cord. Among the insane, too, the variations in this tonic condition follow in a marked way the nutritive changes in the central system, and both facial and bodily expression have a value as an index of the strength and variability of those impulses on which the tone of the skeletal muscles depends. Indeed, so wide in the insane is the variation thus brought about, that when the expressions of the same individual at one time in a phase of mental exaltation and at another in that of mental depression are compared, it appears hardly possible that they can be those of the same person.

This continuous outflow of impulses from the central system is indicated also by the continuous changes within glands, and the variations in these metabolic processes according to the activities of the central system.

Rigor Mortis.—Even in the very act of dying, the influence of these impulses can be again traced. The death of the central nerve-tissues being expressed as a chemical change, causes impulses to pass down the efferent nerves, and these impulses modify those chemical changes which, in the muscles of a frog's leg for example, lead to rigor mortis. It thus happens that a frog suddenly killed and then left until the onset of rigor, will under ordinary conditions show this at about the same time in both legs. If, however, the sciatic nerve on one side be cut immediately after the death of the animal, the beginning of rigor in that leg is much delayed; thus showing that the nervous connection is an important factor in modifying the time of this occurrence (Hermann).

Summary.—In their most general form the activities of the nervous system can therefore be pictured as follows : The peripheral termini of the sensory or afferent nerves are isolated and there pass into the central system at least as many distinct impulses as there are nerves that have been stimulated. The point of entrance of these impulses is in each case the point at which the afferent nerve connects with the cerebro-spinal system, and these points taken all together form a corresponding projection of the sensory surfaces upon the central system. Once entered into the central system and transmitted to the central cells by the collaterals and terminals of the afferent fibre, such an incoming impulse has open to it many pathways among the central cells, and by these pathways it can reach any group of efferent cells. That all the pathways by which it can travel are traversed by it, and that all the efferent cells are in some measure affected, is very probable. Both the diffusion and the response are, however, subject to wide modifications.

The evident response which we commonly regard as the reaction to any stimulus, arises from a more or less localized group of efferent cells and emerges as a series of impulses which pass by the efferent nerves either to find a comparatively limited expression in the contractions of the voluntary muscles or enter into the series of ganglia and plexuses forming the sympathetic system to be distributed in a diffuse manner to the unstriped muscles and the secreting tissues.

In brief, then, the impulses enter the cerebro-spinal system according to the fixed anatomical relation of the afferent nerves. They leave this system

according to similar anatomical restrictions imposed by the arrangement of the efferent cells, and along the efferent pathway they are directed by isolated fibres either to the voluntary muscles, or by means of other fibres to the ganglia of the sympathetic. In this latter subdivision the arrangement is for diffusion from the proximal to the distal members of the series, and here the area of tissue finally affected is large as compared with the part of the efferent system from which the outgoing impulse may have started. Yet the point at which the most significant diffusion of the impulses occurs is the central system.

The afferent elements being single cells only, the amount of diffusion which may occur is limited to the branches of this one group of elements alone. The efferent subdivision of the nervous system, so far as it connects with skeletal muscles, represents a single element, but so far as it is connected with the sympathetic system there are at least two elements arranged in series. The arrangement of the central system, however, is but an elaboration of this latter in so far as the number of elements involved may be increased above two. Any incoming impulse entering the central system at any point tends to be diffused over a large portion of the central cells and by them to all the efferent elements, but the path between the point of the arriving impulse and that at which the evident discharge originates in the efferent cells is variable. The permeability of the central system is therefore inconstant, and probably this inconstancy depends on the one hand on the ease with which the incoming impulses are transferred to it and from it, as well as the ease with which they pass among the elements constituting this subdivision itself. The chief problem in the physiology of the central system is, therefore, to determine how the nerve-impulses find their way among the central cells and at what point they pass over to the efferent cells so as to cause an evident response.

D. Reflex Action.

The simplest and most constant of the co-ordinated reactions of the nervous system are reflex. The term involves the idea that the response is not accompanied by consciousness, and is dependent on anatomical conditions in the central system which are only in a slight degree subject to physiological modifications. This view of reflex activities is in a large measure justified by the facts, but at the same time it must be held subject to many modifications, and it is not possible to make a hard and fast line between reflex and voluntary reactions.

The principal features of a reflex act may be illustrated by following a typical experiment.

Typical Reflex Response.—If the central nervous system of a frog be severed at the bulb, so as to separate from the spinal cord all of the portions of the central system above it, the animal is for a time in a condition of collapse. If, after twelve hours or more, such a frog be suspended by the lip, it will remain motionless, the fore legs extended and the hind limbs pendent, though very slightly flexed. If such a frog were dissected down to the nervous

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system, there would be found the following arrangement: Afferent fibres running from the skin, muscles, and tendons, and forming the dorsal nerve-root with its ganglion. The central mass of the cord in which these roots end, each root marking the middle of a segment. From each segment of the cord go the ventral root-fibres passing to the muscles lying beneath the skin to which the sensory nerves are distributed, as well as to the ganglia of the sympathetic system. The mechanism demanded for a reflex response is an afferent path leading to the cord; cells in the cord by which the incoming impulses shall be distributed; and a third set of efferent elements to carry the outgoing impulses. It is important to consider in detail what occurs in each portion of this reflex arc.

In a frog thus prepared, stimulation of the skin in any part supplied by the sensory nerves originating from the spinal cord causes a contraction of some muscles.

Influence of Location of Stimulus.—The muscles which thus contract tend to be those innervated from the same segments of the cord that receive the sensory nerves that have been stimulated. Thus stimulation of the skin of the breast causes movements of the fore limbs, and stimulation of the rump or legs corresponding movements of the hind limbs. It is noticeable, however, that wherever the stimulus is applied, the hind limbs have a tendency to move at the same time that the muscles most directly concerned contract.

Segmental Reactions.—In attempting to explain this associated contraction of the leg muscles, it must be remembered that the hind limbs are, *par excellence*, the motile extremities of the frog, and therefore all general movements involve their use. We infer from this, moreover, that the arrangement in the spinal cord of the frog is not such that the sensory impulses coming into any segment tend to rouse exclusively the muscles innervated by that segment, but that these incoming impulses are diffused in the cord unevenly and in such a way as to easily involve the segments controlling the legs. As reflex co-ordinating centres, therefore, the several segments of the cord have not an equal value.

When the stimulus is applied on one side of the median plane, the responses first appear in the muscles of the same side, and if the stimulus is slight they may appear on that side only. The incoming impulses are therefore first and most effectively distributed to the efferent cells located on the same side of the cord as that on which these impulses enter. Such a statement is most true, however, when the stimulus enters the cord at the level where the nerves to the limbs are given off. At other levels the diffusion to the limb centres may take place more readily than to the cells in the opposite half of the same segment. When the muscles of the side opposite contract it is found that those there contracting correspond to the group of muscles giving the initial response. The diffusion then tends to be across the cord and to involve the cells located at the same level as that at which the incoming impulses enter it.

There is some reason to think that the path by which the diffusion takes

place is not the shortest one between the two groups of cells, but a path in which the actual crossing of the impulses occurs toward the cephalic end of the cord, so that they must pass up the cord on one side and down on the other.

Strength of Stimulus.—In a reflex response the strength of the stimulus influences the extent to which the muscles are contracted ; the number of muscles taking part in the contraction, and the length of time during which the contraction continues. That the strength of the stimulus influences the extent to which the contraction of a given group of muscles takes place is easily shown when, for example, the toe of a reflex frog which has been suspended is stimulated by pinching it or dipping it in dilute acid. In this case, if the stimulus be slight, the leg is but slightly raised, whereas if the stimulus be strong it is drawn up high. In the same way by altering the stimulus the muscles which enter into the contraction may be only those controlling the joints of the foot, whereas, with stronger stimuli, those for the knee and hip are successively affected, thereby involving a much larger number of muscles. Here, too, we infer a spread of the incoming impulses which is orderly, since the several joints of the limb are moved in regular sequence.

The responses which are thus obtained are not spasmodic, but are contractions of muscles in regular series, giving the appearance of a carefully coordinated movement—a movement that is modified in accordance both with the strength of the stimulus and its point of application. Moreover, such a movement may occur not only once but a number of times, the leg being alternately flexed and extended during an interval of several seconds, although the stimulus is simple and of much shorter duration.

Continuance of Response.—The continuance of the response after the stimulus has been withdrawn must be of course the result of a long-continued chemical change at some point in the pathway of the impulse, and it appears probable by analogy with the results obtained from the direct stimulation of the central cortex, that in these cases the stimulating changes are taking place in the central cells.

Latent Period.—It has been observed that in the case of a reflex frog an interval of varying length elapses between the application of a stimulus and the appearance of a reaction. The modifications of the interval according to variations in the stimulus have been carefully studied. When dilute acid is used as a stimulus, this latent interval decreases as the strength of the acid is increased. When separate electrical or mechanical stimuli are employed, the reaction tends to occur after a *given number* of stimuli have been applied, although the time intervals between the individual stimuli may be varied within wide limits. The experimental evidence for electrical stimuli shows that the time intervals may range between 0.05 second and 0.4 second,[1] while the number of stimuli required to produce a response remains practically constant.

Summation of Stimuli.—A single stimulus very rarely if ever calls forth a reaction if the time during which it acts is very short, and hence there

[1] Ward : *Archiv für Anatomie und Physiologie* (Physiol. Abthl.), 1880.

has developed the idea of the summation of stimuli, implying at some part of the pathway a piling up of the effects of the separately inefficient stimuli to a point at which they ultimately become effective.

The details of the changes involved in this summation and the place at which the changes occur are both obscure, but it would seem most probable that summation is an expression of changes in the relations between the final twigs of the afferent elements and the cell-bodies of the central or efferent elements, which permit the better passage of the impulse from one element to the other, for the evidence strongly indicates that the course of the impulse can be interrupted at these junctions. The foregoing paragraphs are concerned, therefore, with changes occurring in the afferent portion of the pathway.

Next to be considered is the amount of central nervous matter which must be present in the frog's spinal cord in order that the reactions can take place.

Reactions from Fractions of the Cord.—If the construction of the cord was strictly segmental in the sense that each segment contained the associated nerves for a given band of skin and muscle, there should be no disturbance on dividing the cord into its anatomical segments, and practically, among the invertebrates, where the ganglionic chain is thus arranged, the single segments can perform alone all the reactions of which they are capable under normal conditions. In such invertebrates the only change effected by the combination of the segments is that of co-ordinating in time and in intensity the reactions of the series. If, on the other hand, the segments of the cord were more or less dependent upon one another, and not physiologically equivalent, modifications of various degrees would arise according to the segments isolated. It has been found that the spinal cord of the frog may under special conditions be reduced to three segments and reactions still be obtained.

During the breeding season the male frog by means of his fore legs clasps the female vigorously and often for days. If at this season there is cut out from the male the region of the shoulder girdle bearing the fore limbs together with the connected skin and muscles and the three upper segments of the spinal cord, then an irritation of the skin will cause a reflex clasping movement similar to that characteristic for the normal male at this season.[1]

The Efferent Impulses.—Incessantly the efferent impulses pass out from the cord to the muscles and glands. With each fresh afferent impulse those which go out are modified in strength and in their order, but just how they shall be co-ordinated is dependent on so many and such delicate conditions that even in the simplest case the results are to be predicted only in a general way.

The attempt to determine the spread of the impulse in the cord by determining the order in which the various muscles of the thigh and leg contracted in response to thermal stimuli was made by Lombard.[2] In a reflex frog the tendons of the leg and thigh muscles were exposed at the knee, and each attached to a writing rod in so ingenious a manner that simultaneous records of fifteen muscles could sometimes be obtained. The stimulus was a metal

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[1] Goltz: *Centralblatt für die medicinische Wissenschaften,* 1865.
[2] *Archiv für Anatomie und Physiologie,* 1885.

tube filled with warm water at 47° to 61° C., which was applied to the skin. Under these conditions it was remarkable that a continuous stimulus was often followed, not by a single contraction of the muscles, but by a series of contractions, suggesting that in the central system the cells are roused to a discharge and then are for a time concerned with the preparation for sending out new impulses, and that during this latter period the muscles were relaxed.

Apparently a high degree of uniformity in the conditions was obtained in these experiments, but at the same time the reactions were far from uniform, in either the latent time of contraction or the order in which the contraction of the several muscles followed, although certain muscles tended to contract first, and certain series of contractions to reappear. The co-ordination of the contractions is therefore variable in time, even under these conditions. These variations are probably due either to the fact that the impulses are not distributed in the centre in the same manner on each occasion, or if they are thus distributed, the central and efferent cells vary from moment to moment in their responsiveness. That these cells should so vary is easy to comprehend, for all the cell-elements in such a reflex frog are slowly dying. In this process they are undergoing a destructive chemical change, and with these destructive changes are generated weak impulses sufficient to cause their physiological status continually to vary, thus modifying the effects of any special set of incoming impulses acting upon them.

It is not to be overlooked also that the dissection of the muscles tested, and the removal of the skin about them, deprived the spinal cord of the incoming impulses due to the stretching of the skin by the swelling of the contracting muscles and disturbed the order and intensity of such sensory impulses as come in from the tendons and the muscles themselves. However much these impulses may add to the regularity of the muscular responses, as apparently they do, in the case of an intact leg, these experiments indicate that the regularity thus obtained is dependent rather on the constancy of the incoming stimuli than on any fixed arrangement in the nerve-centres themselves. It is thus evident that the discharge of one efferent cell is not necessary in order that another efferent cell may discharge, but that each discharging cell stands at the end of a physiological pathway and may react independently.

Purposeful Character of Responses.—When the muscular responses of a reflex frog to a dermal stimulus are studied, they are seen to have a purposeful character, in that they are often directed to the removal of the irritation. This is demonstrated by placing upon the skin on one side of the rump a small square of paper moistened with dilute acid. As a result the foot of the same side is raised and the attempt made to brush the paper away ; if the first attempt fails, it may be several times repeated. When the irritation has been removed, the frog usually becomes quiet. If the leg of the same side be held fast after the application of the stimulus, or if the first movements fail to brush away the acid paper, then the leg of the opposite side may be contracted and appropriate movements be made by it. Emphasis has been laid by various

physiologists upon reactions of this sort as showing a capability of choice on the part of the spinal cord, thus granting to the cord psychical powers. Against such a view it must be urged that the movements of the leg on the side opposite to the stimulus do not occur until after the muscles of the leg on the same side have responded. When these responses are inefficient because the leg is prevented from moving or because they fail to remove the stimulus, the prime fact remains that the stimulus continues to act and the diffusion of the impulses in the cord goes on, involving in either case the nerve-cells controlling the muscles of the opposite leg. The adjustment of the reaction of the leg, on whichever side it occurs, is, however, far from precise; and although the movements of the leg, when the stimulus is applied far up on the rump, differ from those which follow the application of the stimulus to the lower part of the thigh, yet in either case they are very wide, and in both cases the foot is brushed across a large part of both the rump and leg. Considering, therefore, the rather general character of these movements, and the fact that the movement of the opposite leg only follows after a continued stimulus to the leg of the same side has produced an ineffective response, it is best to explain the result by the diffusion of the impulses within the cord, leaving quite to one side the psychical element. Such reflex actions are in a high degree predictable, but in reality this has little significance, since there is but one general movement that a frog in such a condition can make, whether the stimulus be applied to the toes or the rump—namely, the flexion of the leg—so that under these circumstances the prediction of the kind of movement is a simple matter. The extent of the contraction is related to the intensity of the stimulus, and is in turn dependent on the excitability of the central system, which can be increased or diminished in various ways. The modification of the reaction as dependent on the location of the stimulus can be in a measure predicted, but the modification is wanting in precision just in so far as the movements themselves are wanting in this quality.

Periodic Reflexes.—Not all reflexes are to be obtained from the same animal with equal intensity at different times. In general, frogs in the springtime and in early summer, after reviving from their winter sleep, are highly irregular in their reflex responses—so irregular that students are advised not to attempt the study of these reactions at this season. On the other hand, it is during the spring that the mating occurs, and during this period the male clasps the female and exhibits the peculiar reflex which has already been described. Comparable with this variation in the frog must be the changes which occur in the spinal cords of migratory birds which both in the spring and in the fall are capable of such extended flights, or in the system of hibernating mammals and all animals exhibiting extensive periodic variations in their habits of life.

General Applicability of these Results.—There are many reptiles and fishes in which the arrangement of the spinal cord is more simple than that in the frog; such are the animals in which the actions of locomotion are very uniform, and in which these locomotory actions represent the principal responses of the

muscles whatever the stimulus. In these cases small segments of the body will perform the locomotor reactions when the segments of the spinal cord belonging to them are intact (Steiner).[1] Tarchanow has shown that beheaded ducks can still swim and fly in a co-ordinated manner, and among mammals (dog and rabbit) Goltz and others have demonstrated that if the lumbar region be separated from the rest of the cord by a cut and the animal allowed to recover from the operation, it will with proper care live for many months, and not only are the legs responsive to stimulation of the skin, but the reflexes of defecation and urination are easily induced by slight extra stimulation. An instructive reaction occurs when such animal is held up so that the hind legs hang free. When thus held the legs slowly extend by their own weight and then are flexed together. The reaction becomes rhythmic and may continue for a long time. It is assumed in this case that the stretching of the skin and tendons due to the weight of the pendent legs acts as the stimulus, and in consequence the legs are flexed. This act in turn removes the stimulus, and as a result they extend again, to be once more stimulated and drawn up.

In man, as a rule, death rapidly follows the complete separation of any portion of the cord from the rest of the central system, especially if the separation be sudden, as in the case of a wound. But Gerhardt[2] has recorded the retention of the reflexes in the case of compression of the cord by a tumor, the case having been under observation for four and a half years; and Hitzig[3] a case in which a total separation between the last cervical and first thoracic segments had been survived for as long as seven years. The principal reaction to be observed in such cases is a contraction of the limb muscles in response to stimulation of the skin, such as a drawing up of the legs when the soles of the feet are tickled. No elaborate reflexes are, however, retained in connection with the muscles of locomotion. In the normal individual reflexes involving striped muscles are found in the tendon reflexes, of which the knee-kick is an example, in winking, and the whole series of reflex modifications of respiration, such as coughing, sneezing, and the like.

The activities of the alimentary tract are examples of reflex actions involving the peristaltic contraction of unstriped muscles in deglutition, defecation, and similar peristaltic movements in other hollow viscera. So, too, micturition, the cremaster reflex, emission, and vaginal peristalsis and the reactions of parturition are to be classed here. Moreover, the entire vascular system is controlled in this manner, the contraction and distention of the small arteries being in a large measure in response to stimuli originating at a distance; while as a third group we have the glands, the activity of which is almost entirely reflex.

It thus appears that the reflex responses, namely, simple reactions unaccompanied by consciousness, are in man mainly given by the unstriped muscle-tissue and by glands, and only in a minor degree by the striped muscles. Moreover, while the typical reflex is a reaction over which we cannot exercise

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[1] *Die Functionen des Centralnervensystems der Fische*, Braunschweig, 1888.

[2] *Neurologische Centralblatt*, 1894, S. 502.   [3] *Loc. cit.*

direct control, the normal individual has some power over many of these reactions; for example, the impulse to micturition or defecation can be thus delayed, respiration arrested, and in some instances, so remote a reaction as the beat of the heart either accelerated or slowed at will.

It is of interest to note that many reflexes which in the young are not controlled, as micturition for instance, become so gradually—a change most probably dependent on the growth of neurons from the cephalic centres into the cord, thus subjecting the cord-cells to a new set of impulses which modify their reactions. That such is the case is indicated by the fact that extreme fright or anæsthetics which diminish the activities of the higher centres often cause these reactions to take place involuntarily. Other reflexes are present in early life, but disappear later; such are the sucking reflex of an infant, and the remarkable clinging power of the hands, by which a young child is enabled to hang from a bar, thus supporting the weight of its entire body, often for several minutes. This last capacity soon begins to wane, and usually disappears by the second month of life (Robinson, *Nineteenth Century*, 1891).

The Nervous Background.—We return now to the conditions which modify the spread of the impulses within the central system, when this system is represented by the spinal cord of a reflex frog. Admittedly, there is here present but a fraction of the central system. It has been shown that all incoming impulses tend to spread over a large part of the central system. In a reflex frog, therefore, the cord is cut off from the remote effects of impulses which normally enter the system by way of cells located in the portion removed. Moreover, in the complete nervous system, the incoming impulses tend to be transmitted to the cephalic end, and in some measure give rise to impulses returning within the central system and affecting the efferent cells. In a fragment of the central system like the cord, such impulses taken up by the central cells must pass so far as the neurons are intact, but as these end at the level of the section, such impulses are lost, in the physiological sense, at that point.

The fact, therefore, that the experiments with spinal reflexes are conducted on a portion of the central system has two important physiological consequences. In the first place, there are wanting incoming impulses, direct or indirect, from the portion removed; on the other hand, through the section of the afferent neurons, in their course within the central system, there is a direct diminution in the number of the pathways by which the impulses arriving at the cord may be there distributed. It is most probable that in the frog, at least, the reduction of the central mass does not so much diminish the number of pathways by which the impulses may be immediately distributed by way of the afferent and central elements, as it diminishes the number of impulses which by way of the portion removed arrive at the efferent cells and modify their responsiveness.

The modification of the responsive cells under more than one impulse is well illustrated by an experiment of Exner:[1] A rabbit was so prepared that an

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[1] *Archiv für die gesammte Physiologie*, Bd. xxvii.

electric stimulus could be applied to the cerebral cortex at a point the excitation of which caused contraction of certain muscles of the foot. One of these muscles was attached to a lever so that its contraction could be recorded, and a second electrode applied to the skin of the foot overlying the muscle. The discharging efferent cells in the cord were in this case subject to impulses from two directions, one from the cortex and one from the skin of the foot. With a current of given strength stimulation of the cortex alone caused a contraction of the muscle, and stimulation of the skin of the foot alone, a similar contraction. When both were stimulated simultaneously, the extent of the contraction was greater than when either was stimulated alone. If now the strength of the stimulus applied to the skin was so reduced that, alone, it was inefficient, then a stimulus from the cortex, which produced a reaction, as indicated by the first cortical stimulus in Figure 172 (A, a), put the efferent
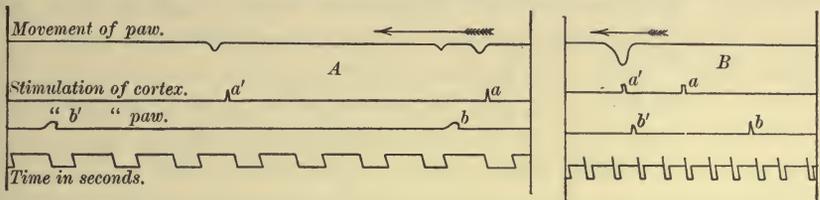
FIG. 172.—To show the reinforcing influence of stimuli applied to the cerebral cortex and to the skin of the paw, on the movements of the paw of a rabbit (Exner). The arrows indicate the direction in which the curves are to be read. In curve A the cortical stimulus at a causes a movement of the paw. Dermal stimulus, within a second, at b causes a movement of the paw. Cortical stimulus at a' causes a movement of the paw. Dermal stimulus several seconds later at b' is ineffective. In curve B dermal stimulus at b is ineffective. The cortical stimulus at a several seconds later is also ineffective. The dermal stimulus at b' is ineffective, but if followed within 0.13 second by a cortical stimulus at a' a movement of the paw occurs.

cells in such a condition that the stimulus from the skin (A, b) Figure 172, applied within 0.6 second, produced a second contraction of the muscle, although, alone, the stimulus from the skin had proved inefficient. Here the first efficient stimulus from the cortex had rendered the discharging cell, for a short period of time, more excitable. In the same figure the record shows that if a longer interval, here more than three seconds, be allowed to elapse, then the second stimulus from the skin remains inefficient. A similar relation between the two incoming impulses is also found to hold, when the stimulus from the skin is made to precede. The curve B, Fig. 172, shows the results when both stimuli are inefficient. In this the stimuli (b and a) produce no effect when given several seconds apart, but when they occur within a short interval (b' and a')—in this case 0.13 second—a contraction of the muscle follows. These various experiments, taken together, show in a beautiful way that in the cases chosen the two sets of impulses tend to reinforce each other, whether they are efficient or inefficient, and without regard to the order in which they come.

This relation between the discharging cell and those by way of which it is stimulated can be illustrated in still another way. It was observed by Jendrassik [1] that when a patient was being tested for the height of his knee-kick,

[1] *Deutsches Archiv für klinische Medicin*, Bd. xxxiii.

a voluntary muscular contraction, or an extra sensory stimulus occurring about the same time that the tendon was struck, had the effect of increasing the height of the kick.   This was studied in detail by Bowditch and Warren,[1] and they were able with great exactness to measure the interval between the contraction of the muscle used for reinforcement and the time at which the tendon was struck.   The curve shown in Fig. 173 represents the results of these experi-
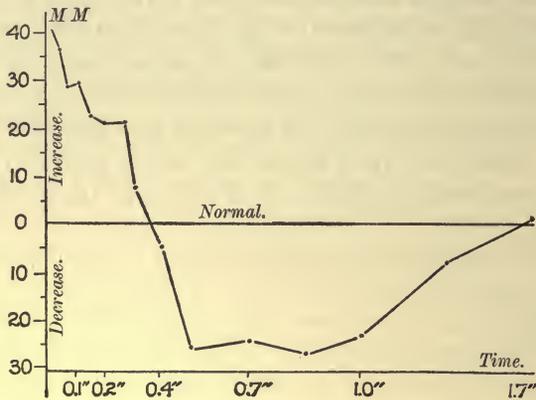
FIG. 173.—Showing in millimeters the amount by which the "reinforced" knee-kick varied from the normal, the level of which is represented by the horizontal line at 0, "normal."   The time intervals elapsing between the clenching of the hand (which constituted the reinforcement) and the tap on the tendon are marked below.   The reinforcement is greatest when the two events are nearly simultaneous. At an interval of 0.4″ it amounts to nothing; during the next 0.6″ the height of the kick is actually diminished the longer the interval, after which the negative reinforcement tends to disappear; and when 1.7″ is allowed to elapse the height of the kick ceases to be affected by the clenching of the hand (Bowditch and Warren).

ments.   It indicates that in general the closer together these two stimuli occur, the greater the reinforcement.   At an interval of 0.4 second no effect is produced by the muscular contraction.   Increasing the interval only very slightly has, however, the effect of greatly diminishing the height of the knee-kick— *i. e.* decreasing the strength of the discharge of the efferent cells—and this effect is not lost until the interval is increased to 1.7 second, when the voluntary muscular contraction ceases to modify the response.   A given efferent cell is thus modified in its discharge according to the several stimuli that act upon it.

Effects of Disuse.—Studies on inactivity show that a certain amount of exercise in any given cell is necessary for its proper nutrition, and if the excitation fall below the point which causes this, the responsiveness of the cell is diminished.

For example, a strychnized reflex frog on being dipped into a solution of cocaine loses in so large a measure its irritability that its responsiveness falls far below that of a normal frog.[2]   In this case the central system is deprived by the action of the cocaine of the impulses which even in the absence of any special form of irritation normally arrive from the skin, and the abolition of these impulses causes a diminution in central responsiveness.   Effects which

[1] *Journal of Physiology*, 1890, vol. xi.
[2] Poulsson: *Archiv für Pathologie und experimentelle Pharmakologie*, 1885, Bd. xxvi.

can thus be accomplished in a few seconds by cutting off the afferent impulses from the skin may of course follow any slow diminution in these impulses, although all such slow changes are much more likely to be accompanied by some sort of compensation whereby other afferent impulses in a measure take the place of those which have been suppressed. The loss of these impulses which rouse the cells to activity is usually a more important condition than direct nutritive change, and must for this reason always be kept in view.

Inhibition.—On the other hand, let one leg of a reflex frog be stimulated in the usual manner by pinching or by acid, and then the experiment repeated, while the other leg is lightly pinched at the same time, and it will be found that either the latent period preceding the response is increased or, with the strength of stimulus employed, the reaction does not occur. This is an example of inhibition which can be caused by the simultaneous excitement of a nerve-cell in several ways.

To obtain inhibition there must be at least two pathways by which impulses reach a given cell, and the two stimuli must tend to excite *different* reactions. When they tend to excite the *same reaction* a reinforcement follows. The inhibition, therefore, is connected with the effect of these two sets of impulses upon the responding cell, and that is always associated with the fact that as the two paths end in different relations to the cell, the impulses must enter it at different points, and hence in the first instance tend to act on different portions of the cell-contents.

Though at the present time it is not possible to give a theory of inhibition that will be general and satisfactory, there is enough known to indicate that this effect, when developed in the central nervous system, is not produced by a special set of nerve-fibres, but is the result of the action of several incoming impulses, arriving by different paths, on the responsiveness of a given cell.

E. Voluntary Actions.

On attempting to distinguish between a voluntary and reflex act from the physiological standpoint, we find the chief difference to be that the voluntary act is not predictable, because, according to the capabilities of the animal, it may be more variable in form than is the reflex response, and also because, instead of occurring within a short interval after the stimulus, as does the reflex, the voluntary response may be delayed even for years. For example, we read in a book some statement that makes us desire to question the author. The question is a response to the stimulus given by the printed page, and it may be carried out by writing a letter within a few hours, or delayed until a meeting with the author years hence. During this interval, and in the absence of the author, the reaction which will take the form of a question remains incomplete, while his presence is sufficient to set in motion the train of stimuli which shall cause it. Moreover, consciousness enters as an element into such reactions, and there is present a mental image of the act to be accomplished, together with some remembrance of its execution.

For the most complex voluntary reactions the entire central system is necessary, and especially the cortex of the cerebral hemispheres, while it has already been shown that the impulses which cause reflex actions can make their circuit in a very limited portion of the spinal cord. In the case of voluntary reactions the impulses take a longer pathway and involve a larger number of nerve-elements, since from the point at which they enter the system they must pass to the cephalic end. At the same time, in a voluntary reaction a greater number of impulses combine to modify the discharge from the efferent cells.

Tracts in the Central System.— How this result is accomplished has been studied both in mammals and in man. Histology shows us the fibres of the dorsal root entering the cord and sending one branch cephalad and the other caudad, both branches giving off collaterals (Fig. 174). In man and the higher mammals the dorsal root-fibres enter the cord in three groups—a median group, an intermediate group of large fibres, and a lateral group of very fine fibres, the bundle of Lissauer. When the dorsal root is sectioned between the ganglion and the cord, all these fibres degenerate.

FIG. 174.—Schema showing pathway of the sensory impulses. On the left side S, S′ represent afferent spinal nerve-fibres; C, an afferent cranial nerve-fibre. This fibre in each case terminates near a central cell, the neuron of which crosses the middle line and ends in the opposite hemisphere (van Gehuchten).

The degeneration extends in the dorsal columns down the cord two or three centimeters from the level of the section, and also up the cord as far as the nuclei of the dorsal columns, located at the commencement of the bulb. If the section is made near the caudal end, the degeneration may in consequence run through the entire length of the cord. Moreover, it occurs only on the side of the cord to which the sectioned nerves belong. Take, for example, the area of degeneration caused by the section in a dog of the dorsal roots on the left side between the sixth lumbar and second sacral nerves. The degeneration in the lower lumbar region is represented in Figure 175, A, in the upper lumbar region in B, and in the thoracic in C. On passing cephalad the area of degeneration becomes smaller. This is interpreted to mean that all along, between the caudal and cephalic limits, fibres are given off from the main bundle to the intermediate segments of the cord. Here is evidence of an arrangement that is always to be kept in view. Though a

number of fibres among those degenerating after section of the dorsal roots may run the longer course, the larger portion run a short or an intermediate course, and are therefore distributed at different points between the termini. Injury to the dorsal roots at different levels shows, moreover, that the fibres
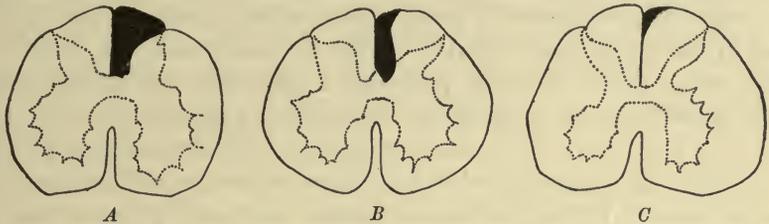
Fig. 175.—Sections showing the degeneration in the dorsal columns of the dog's spinal cord when the dorsal roots from the sixth lumbar to the second sacral have been cut on the left side (Singer): *A*, level of the sixth lumbar; *B*, level of the fourth lumbar; *C*, level of the sixth thoracic. Degenerated area in black.

from a given level which run the length of the dorsal columns do not mingle indiscriminately with those from other levels, but form a bundle, and that this bundle in the cephalic part of the cord tends to lie nearer the middle line the more caudad the level from which it arises.

From these relations it is evident that comparatively few of the dorsal root-fibres run the entire length of the dorsal columns. If, then, it is remembered that in describing the arrangements of the cord emphasis is usually placed on the very short pathways formed in part by collaterals and concerned in the simpler reflexes, and on the longest pathways concerned in the voluntary reactions, as two extremes between which are to be found a more or less complete series of intermediate arrangements, the unevenness of the presentation can be corrected.

Since these fibres in the dorsal columns of the cord degenerate on destruction of the dorsal roots, it is inferred that they must be morphologically continuous with certain fibres in the roots, and, since the dorsal roots are afferent pathways, they too must form part of the afferent pathway in the cord.

It is of course a portion only of the afferent pathway that is thus formed, for both the intermediate and lateral groups of root-fibres enter the gray matter of the dorsal horn, and must there come into physiological connection with other nerve-cells both central and efferent. The fact that the connection is only physiological accounts for the arrest of the Wallerian degeneration at these points after section of the dorsal roots.

The continuation of the paths for the afferent impulses must therefore be formed by the neurons of the central cells with which the dorsal root-fibres connect.

Degeneration after Hemisection of Cord.—Upon hemisection of the cord involving one lateral half the ascending fibres which degenerate appear in the dorsal columns, in the dorso-lateral ascending tract, and in the ventro-lateral ascending tract. The number of degenerated fibres is large on the side of the lesion, but on the opposite side there are also degenerated fibres in all

these localities, although they are by no means so numerous. It is inferred that all the fibres which thus degenerate form paths for the afferent impulses.

The impulses which come in over a dorsal root on one side can therefore find their way cephalad either by the direct continuations of the dorsal root-fibres running in the dorsal column of the same side, or by way of central cells in the lateral column of the same side of the cord, and also to a less degree in the lateral and dorsal columns of the opposite side.

The tracts which undergo Wallerian degeneration after this treatment include, therefore, those formed by the neurons arising from central cells. These cells have their cell-bodies arranged in a column running the length of the cord. In the neighborhood of this column some of the dorsal root-fibres terminate. In the bulb we are familiar with such groups of cells, well marked as the "nuclei of the sensory nerves," and these cells in the cord, though far less clearly segregated, are the homologues of those in the bulb. If this is granted, then the fibres which are continued from these central cell-groups, whether in the cord or bulb, are also homologous.

Corroborative of what has been said on the subject of afferent pathways in the cord are the results of Pellizzi.[1] He studied dogs, making use of the method of Marchi, whereby the nerve-sheaths of fibres beginning to degenerate or the nutrition of which is disturbed give a characteristic reaction ; he found, after hemisection of the cord, the same lesions that have been described above, with the addition that the changes could also be followed in some of the fibres of the ventral roots. More significant, however, is the fact that section of the lumbar and sacral dorsal roots, without direct injury to the cord, gave rise to modifications of the medullary sheaths, detectable by the method of Marchi, in all the localities just named.

A distinction must be made at this point. Wallerian degeneration in the central system means eventual destruction of the severed fibre. The method of Marchi shows a characteristic change in fibres entering upon this degeneration, but this method also shows changes in the sheaths of elements which are only physiologically connected with those about to undergo Wallerian degeneration, but which themselves are, as a rule, not ultimately destroyed. Under the usual conditions of experiment Wallerian degeneration is confined within the morphological limits of a single cell-element, but the physiological changes in the cells overstep this limit, as shown by Marchi's reaction. It is proper to add, also, that Wallerian degeneration may under some conditions extend to a group of nerve-cells only physiologically connected with those suffering the initial injury.

Physiological Observations on Afferent Pathways.—Making use of the fact that strong stimulation of the sensory fibres, such as those in the sciatic nerve, causes a rise in blood-pressure, Woroschiloff[2] sought to block the passage of the impulses causing this reaction by section of the cord in different ways in the upper lumbar region of the rabbit. It appears that in

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[1] *Archives Italiennes de Biologie*, 1895, Bd. xxiv.
[2] *Berichte der math.-phys. Classe d. k. Gesellsch. d. Wissen. zu Leipzig*, 1874.

this animal the reaction was most diminished—that is, stimulation of the sciatic produced least rise in the blood-pressure—when the lateral columns of the cord had been cut through; and that the effect of section of the lateral column on the side opposite to that on which the stimulus was applied was greater than that following section of the column on the same side. These experiments are open to the criticism that the results are proved only for a very limited set of conditions, and hence it would be unwise to make any broad inference from them; yet at the same time they form a very definite part of the evidence which directs our attention to the lateral columns of the cord as a principal afferent pathway.

The physiological observations of Gotch and Horsley [1] indicate that when in a monkey a dorsal root is stimulated electrically, then 80 per cent. of the impulses pass cephalad on the same side of the cord, while the remainder cross. Of the 20 per cent. that cross, some 15 per cent. pass up in the dorsal columns. The dorso-ventral median longitudinal section of the cord in the monkey (sixth lumbar segment) [2] shows an ascending degeneration in a small part of the dorsal area of the direct cerebellar tracts and of the ventro-lateral tracts, as well as in the columns of Goll. This would indicate that the section had cut fibres which crossed the middle line and ran cephalad in these localities.

These investigations all point to the several tracts most closely connected with the dorsal nerve-roots as the paths for the sensory impulses. The experimental results, taken together, are by no means accordant, but not necessarily mutually exclusive: confusion must, therefore, not be permitted to enter here through any unwarranted attempt to combine observations which should really be kept apart, and the failure of which to harmonize is in large degree an expression of the physiological complexity of the cord.

Osawa [3] found that when the cord in a dog was hemisected (in the upper lumbar or lower thoracic region) the animal showed for the most part no permanent disturbance of sensation or motion.

If the cord is first hemisected on one side, and later on the other side, the second hemisection being made a short distance above or below the first, sensation and motion persist behind the section, although they are somewhat damaged. After three hemisections, alternating and at different levels, there still remained a trace of co-ordinated movement possible to the hind legs, although the sensibility of the parts could not be clearly demonstrated. The path thus marked out for any afferent impulses is certainly a tortuous one. These observations were followed by a number of others, the most important of which in this connection are the following:

Section of all parts of the cord except the two lateral columns (in the lower thoracic region, Fig. 176) was without influence on the sensibility or movements of the hind legs. After section of the entire cord, with the exception of the dorsal and ventral columns and the intervening gray matter, sensation was

[1] Croonian Lectures, *Philosophical Transactions Royal Society*, 1891.

[2] Grünbaum: *Journal of Physiology*, 1894, vol. xvi.

[3] *Untersuchungen über die Leitungsbahnen im Rückenmark des Hundes*, Strassburg, 1882.

nearly destroyed, while the voluntary movements of the leg were but slightly disturbed (Fig. 177). After section of the entire cord, with the exception of the dorsal columns, both sensation and motion were lost (Fig. 178).
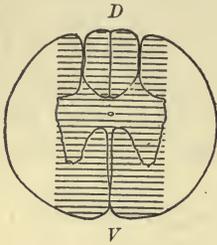
FIG. 176.—Outline of the spinal cord of a dog; the shaded portion indicates the extent of the lesion. The lateral columns of the cord are intact (Osawa).
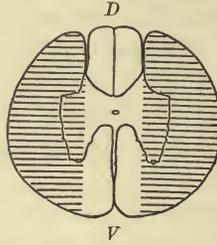
FIG. 177.—Outline of the spinal cord of a dog; the shaded portion indicates the extent of the lesion. The dorsal and ventral columns, together with the intermediate gray matter, are intact (Osawa).
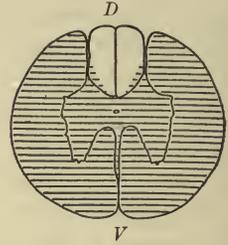
FIG. 178.—Outline of the spinal cord of a dog; the shaded portion indicates the extent of the lesion. The dorsal columns alone are intact (Osawa).

Here are a number of very striking results. It is to be noted that the lateral columns of the cord form the important pathway for all the impulses which influence sensation and motion caudad to the section, but, at the same time, section of them causes a marked diminution of sensation alone. On the other hand, the preservation of the dorsal columns alone does not preserve sensation.

It will be understood, of course, that the motion in question is executed by muscles lying caudad to the section and is co-ordinated with that of the structures lying in front of it. Similarly sensation was inferred from movements executed in front of the level of the section and caused by stimulation behind it.

A double hemisection of the spinal cord as described above seems to involve an interruption of all the long pathways. Yet the nervous impulses pass such a block in *both* directions. Probably within the central system as elsewhere the amount of information conveyed is not directly dependent on the number of nerve-fibres stimulated. In general, a very small number—those brought into action by pulling out a single hair—are as efficient in co-ordinating our responses as would be the stimulation of a thousand times the number. Such being the case, it is not impossible that although after the sections of the cord both the number and intensity of the impulses that pass the point of section may be diminished, yet they may still remain sufficient to modify the reactions of the caudal portion of the cord, which is in no very great degree dependent on such modifying impulses. That the impulses may pass along a cord twice hemisected on opposite sides demands the aid of the gray matter, and we at once refer to the short fibre-tracts as the pathway.

It is a drawback to such a view that physiologists have not been accustomed to lay much weight on the connections established by these short tracts, but from the anatomical side there is no inherent difficulty in accounting for many

reactions by means of them. It is evident that, so far as the dog is concerned, the long and preferred pathways in the spinal cord are by no means the only pathways, and, though probably the human cord offers fewer possible alternatives, the arrangement is presumptively according to the same plan.

Specific Nerves.—In order to analyze the afferent pathways still further, we next inquire whether among the dorsal nerve-roots which pass between the cord and periphery there are separate nerve-fibres for each of the modes of sensation represented by pressure, heat, cold, pain, and the muscle-sensation. The data available for determination of this question are not of the best, but are still of some value.

The number of dorsal root nerve-fibres on both sides was found (in a woman twenty-six years of age) by Stilling to be approximately 500,000, which is probably an underestimate.[1] The area of the skin in a man of 62 kilograms (136 pounds), and twenty-six years of age, was found by Meeh to be 1,900,000 square millimeters.[2] Taking three-fifths of the number of the dorsal root-fibres (300,000) as the portion going to the skin, the other two-fifths going to the muscles and joints, there is evidently one nerve-fibre to innervate, on the average, about 6 square millimeters of skin.

It is recognized that dermal innervation is extremely unequal, as the experiments on tactile discrimination and the like all indicate. The average distribution which has just been suggested must therefore be subject to local modifications that are very wide. Moreover, Woischwillo[3] has determined that in man the skin of the arm is three times better supplied with sensory nerves than that of the leg. In both arm and leg the relative abundance of the sensory nerves increases toward the extremity of the limb. This increase is specially marked in the leg. Assuming, however, one nerve-fibre to 6 square millimeters to be the average relation, it becomes a serious matter to postulate separate groups of fibres for each mode of dermal sensation, since each time a new set of fibres is admitted the area of the skin innervated by any one fibre with a given function is thereby increased.

The histological evidence for the area of skin innervated by a single sensory fibre has still to be gathered, but in the mean time physiological observations indicate that the area controlled by a single fibre cannot be indefinitely extended, and the suggestion of a new category of nerve-fibres needs very ample evidence to make it plausible. This being the case, there is good reason to limit the number of categories of nerve-fibres.

In every case the fibres carrying the impulses which come from the skin arise as outgrowths of the spinal ganglion-cells. Trophic nerves as a special category are not recognized, nor reflex nerves, the functions attributed to the latter being now explained by the collaterals of the afferent fibres. At present it is sometimes maintained that there must be special nerves for pain, pres-

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[1] Stilling: *Neue Untersuchungen über den Bau des Rückenmarks,* Cassel, 1859.

[2] *Zeitschrift für Biologie,* 1879, Bd. xv.

[3] "Ueber das Verhältniss des Kalibers der Nerven zur Haut und den Muskeln des Menschen," *Inaug. Diss.* (Russian), 1883, vide *Centralblatt für Nervenheilkunde,* 1883, Bd. vi.

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sure, heat, and cold. The evidence for those of pressure and heat and cold is the most satisfactory.

Pain.—Upon severe stimulation of the skin or muscles the normal person experiences a distinct sensation of pain. There is, however, great variation in the intensity of this sensation when the same stimulus is applied to different persons.

If we include abnormal persons, it is found that while in a few cases complete absence of painful sensations has been noted—the other sensations remaining normal—there are at the other end of the scale those cases in which pain is produced by many stimuli, which would not have this effect on persons in ordinary health. The capability of a given stimulus to produce pain is therefore subject to wide variations according to the general condition of the subject.[1] The same stimulus has different effects in a given individual according to several circumstances. Peripheral irritation, such as an inflammatory process in the skin, greatly increases the intensity of the pain caused by the stimulation of the nerves supplying the locality. Continued stimulation of the sensory nerves of the muscles and viscera has the same effect.[2] Local anæsthetics, such as cocaine, may reduce the sensibility to zero, and the same follows the general anæsthesia produced by chloroform, ether, nitrous oxide, morphia, and similar drugs. Painful sensations are distinct and powerful only when the stimulus is applied to general sensory nerve-trunks—i. e. those mediating cutaneous, muscular, and visceral sensibility—while the nerves which mediate the special sensations of light, sound, taste, and smell do not give pain even on excessive stimulation.

Limiting our observation, therefore, to the nerves of cutaneous sensibility, it is found that the sensations of pressure, heat, and cold may all be present to a normal degree, and yet increasing the stimulus be without effect in causing any painful sensations whatever. This would represent a condition of complete analgesia. Moreover, the capacity of the skin to cause abnormal painful sensations upon the adequate stimulation of each of these groups of nerves may be associated (in lesions of the central system) with any one group alone, the abnormal pain-sensations thus produced being either those of excess or deficiency.

We advance the hypothesis, therefore, that each of these three sensations, if pushed to excess, is usually accompanied by pain of gradually increasing intensity. Therefore it is most probable that these nerves when slightly stimulated mediate their proper sensations, but when this stimulus is pushed to excess they can give rise to pain also, and that in the last instance this sensation of pain may prove exclusive of any other. If this view is correct it appears improbable that special pain-nerves exist.

As various experiments show, increasing either the strength of the peripheral stimulus, the number of fibres to which it is applied, or the irritability of the terminals of the fibres, will assist in arousing painful sensations. In the

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[1] Strong: *Psychological Review*, 1895, vol. ii. No. 4.
[2] Gad und Goldscheider: *Zeitschrift für klinische Medicin*, Bd. xx.

last analysis the physiological condition for pain is excessive stimulation, which by all analogy must mean excessive discharge within the central system. The changes following this discharge into the central system are not such as lead to co-ordinated muscular responses, but to convulsive reactions of a very irregular character. Where this process takes place in the central system we do not know, because we can only determine the existence of this sensation when conscious. As to normal analgesia, it must be looked upon as dependent on a condition in which excessive stimulation cannot be produced; and we find this condition normally present in the case of the nerves of special sense.

Returning now to the arrangements by which the several dermal sensations are mediated, the hypothesis may be entertained that one peripheral twig of a dermal nerve may be modified for thermal and another for mechanical stimulation, and, though they run by way of the same ganglion-cell, may yet find a different distribution in the centre, and thus lead to different sensations.

Since in the pathological cases the one sort of sensibility may be lost while the others remain, it has been inferred that there were separate fibres for the conveyance of each sort of sensation. This idea was expressed in the law of the specific energies of nerves as formulated by Johannes Müller, who pointed out that in many cases the same nerve might be stimulated in any way, mechanically, electrically, or chemically, as well as in the normal physiological manner, and that in all cases the mode of the response was the same—a sensation of light or taste or contact, as the case might be. Hence it was argued that the mode of the sensation was independent of the kind of stimulus, but dependent on the nature of the central cells, among which the afferent fibres terminated. It will be seen, however, that this argument does not touch the character of the nerve-impulses in any two sets of nerves, and we have no observations by which to decide whether the nerve-impulses passing along the optic nerve-fibres are, for example, similar or dissimilar so those which pass along the auditory fibres.

If the nerve-impulses are always all alike, there seems no escape from the inference that separate nerve-fibres convey the different sorts of impulses to the cord. At the same time, it is just possible that the nature of the impulses and of the resultant sensation is, in the nerves of cutaneous sensibility, determined by the form of the peripheral stimulus, and that, as a consequence, different branches of the same nerve-fibres may be conceived of as susceptible to different forms of stimulation, and thus the two different sensations follow from the partial stimulation of the same nerve-fibres.

Pathway of Impulses in the Spinal Cord.—The question arises how these impulses are distributed among the afferent tracts which are recognized in the cord, and whether these tracts form special paths for the impulses that rouse the several sensations of pressure, temperature (heat and cold), and pain. Since it is necessary to know the sensations of the subject, this problem can be, in some ways, best studied in man. Here, owing to wounds or disease, it may so happen that some of these sensations are lost or greatly diminished, and it is to be determined whether this loss is constantly associated with the inter-

ruption of definite tracts. Unfortunately, however, the material for such a study is very meagre.

The weight of evidence indicates that the result of a lesion in one lateral half of the spinal cord in man and in the higher animals is followed by a loss or impairment of motion on the same side, and a loss of sensation which is greatest on the side opposite to the lesion. As just cited, there are cases in dogs where the damage caused by the hemisection is apparently transient, and no permanent loss can be demonstrated, but in man the loss of function tends to be, far more persistent.

On the basis of a case [1] in which the lateral column of the cord and the gray matter of both horns on the same side was the seat of damage, and in which there was a total loss of pain on the opposite side of the body without impairment of tactile sensibility, it may be inferred that the pain-impulses cross soon after entering the cord, and pass cephalad by some path lying within the damaged area. A second case [2] is recorded in which a stab-wound divided all of one-half of the cord plus the dorsal column of the other half. There was here a loss of sensibility to pain on the side opposite the lesion, together with the loss of tactile sensibility on both sides, pointing, therefore, to the dorsal columns as the paths for the tactile impulses.

The observations of Turner [3] on monkeys, in which hemisection of the cord had been made in the lumbar and thoracic regions indicate that all sensory impulses cross immediately after entering the cord, yet section in the cervical region showed that the impulses roused by touching the skin pass in part on the same side of the cord as the section, the other sensory impulses being, however, completely crossed.

On the other hand, from his work on hemisection of the dorsal cord of the monkey at different levels,[4] Mott found the disturbance of sensibility of all forms mainly on the side of the section. The evidence for the path of the cutaneous impulses is therefore contradictory.

In addition to the cutaneous impulses there are the sensory impulses from the viscera, muscles and tendons, which find their path cephalad probably along the direct cerebellar tract as well by the other pathways conducting cephalad. After hemisection of the cord the " muscular " sensations are usually lost on the side of the section.

Since, then, the dorsal and lateral columns of the cord appear to contain the chief afferent paths for the sensory impulses, the next step in following the pathway is to find the terminations of these tracts.

The long tracts in the dorsal columns are connected with the nuclei of those columns (nuclei of Goll and of Burdach) on the same side. The cells of these nuclei send their neurons cephalad ; in part they decussate in the sensory crossing and contribute to the formation of the lemniscus, by way of which they pass either directly to the cerebral cortex or reach this only after

[1] Gowers : *Clinical Society's Transactions*, 1878, vol. xi.
[2] Müller : *Beiträge zur pathologische Anatomie und Physiologie des Rückenmarkes*, Leipzig, 1871.
[3] *Brain*, 1891.   [4] Mott : *Journal of Physiology*, 1891, vol. xvii.

interruption in the thalamus.[1]   Fig. 179, as will be observed, shows no fibres running directly to the cortex without interruption in the thalamus.   It will
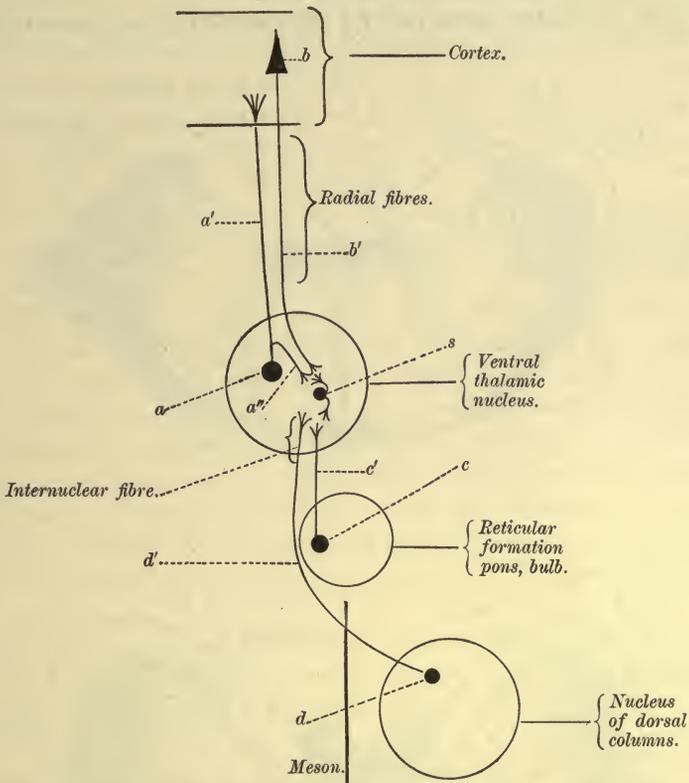
FIG. 179.—To illustrate the pathway of a sensory impulse arriving at the nuclei of the dorsal columns "*d*" or the gray matter of the pons and bulb "*c.*" The impulse is represented as passing over to a new element "*a*" in the thalamic nuclei, and from thence to the cortex. In the other direction the cortex is shown as connected with the thalamic cells by the neuron *b';* only the fibres arising from the nuclei of the dorsal columns cross the middle line "meson" (von Monakow).

be noted that these fibres of the dorsal columns are physiologically joined with the contralateral thalamus and hemisphere. In part, however, the neurons from the dorsal nuclei enter the cerebellum by the inferior peduncle of the same side. The ascending fibres in the lateral columns of the cord pass to the cerebellar hemisphere of the same side by way of the inferior peduncle of the cerebellum, and, although the paths out of the cerebellum are not clearly marked, the general relation of the hemispheres of the cerebellum to that of the cerebrum is a crossed one. Some of the fibres by which this crossed connection is accomplished pass from the cerebral hemisphere along the crus of the same side to the olivary body, and thence by way of the arcuate fibres of the pons and the middle peduncle to the opposite cerebellar hemisphere.

It is with the "motor" region of the cerebral hemisphere that this connection of the cerebellum appears to be most marked. If this really repre-

[1] von Monakow : *Archiv für Psychiatrie und Nervenkrankheiten,* 1895, Bd. xxvii.

sents the path for the sensory impulses finding their way by the antero-lateral tract, then the impulses are finally delivered to the hemisphere on the same side of the system as that on which they enter.

The direct cerebellar tracts pass by the way of the restiform body to the
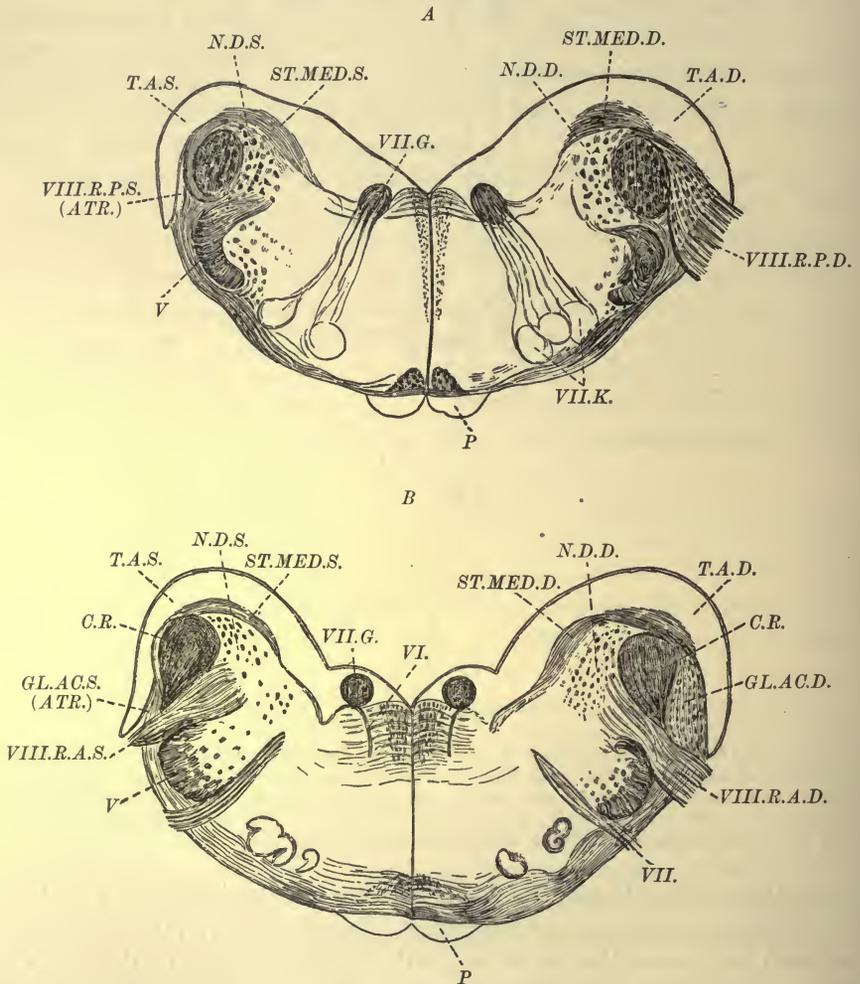
FIG. 180.—Sections of the bulb of a rabbit after lesion of the cochlear portion of the eighth nerve (Onufrowicz): *A*, section at the level of the posterior root of the eighth nerve; *B*, section at the level of the accessory ganglion of the eighth nerve. In the designations the final *S* = "left" and the final *D* = "right." *C.R*, restiforme; *N.D*, dorsal nucleus; *P*, pyramids; *St. Med*, striæ medullares; *T.A*, tuberculum acusticum (atrophied on the left side); *Gl.Ac*, accessory ganglion (atrophied on the left side); *VIII.R.P*, posterior root of the eighth nerve (atrophied on the left side); *VIII.R.A*, anterior root of the eighth nerve; *VII.G*, knee of the seventh nerve; *VII.K*, nucleus of the seventh nerve; *V*, root of the fifth nerve.

middle lobe of the cerebellum, mainly on the same side; from here, by way of the superior peduncle, there is a crossed connection with the more cephalic cell-masses.

On passing up the axis the sensory cranial nerves appear. Those which depart most from the type of the dorsal spinal nerves are the eighth or audi-

tory, the second or optic, and the first or olfactory ; and these require special comment.

Eighth Nerve, Hearing.—The eighth nerve goes to the ear. The ganglion-cells appear in two groups, the accessory ganglion *Gl.Ac.* and the spiral ganglion of the cochlea. This latter is definitely associated with the cochlear branch of the auditory nerve which has to do with the organ of Corti. The other branch of the auditory nerve, the vestibular, is associated with the semicircular canals, the functions of which are not auditory, but concerned with the maintenance of equilibrium (see Fig. 180).

The branch for the semicircular canals and that for the cochlea have different central connections.[1] The auditory fibres proper arising from the cells of the spiral ganglion in the cochlea and from those of the anterior auditory nucleus (*Gl. ac.*), first connect with the cells of the tuberculum acusticum (*T.A.*), and are thence continued by the striæ acusticæ (*St. med.*) into the lemniscus of the opposite side ; through this with the posterior quadrigeminum and the internal geniculate body of that side, probably the thalamus also, and thence by the internal capsule toward its occipital end, with the cortex of the more occipital portions of the first and second temporal convolutions.

This path is indicated by comparative anatomy (Spitzka), by experimental degeneration practised on animals (von Monakow), and by pathological observations on man where the pathway has become injured or diseased in one of its parts.

By the two latter forms of evidence it appears that the portion of the cerebral cortex is also associated with the lateral nucleus of the thalamus of the same side, for injury to the cortex causes atrophy of this part of the thalamus.

Second Nerve, Optic.—As has long been recognized, the optic nerve, so called, is a cerebral tract morphologically equivalent to such tracts as connect any portion of the cerebral cortex with a primary centre, the retina being in part the representative of the cerebrum, and the pulvinares, the quadrigemina, and geniculata externa being the primary centres.

At the chiasma where the two optic nerves come together their fibres intermingle, and then emerge as the optic tracts, which contain not only the fibres connected with the retina, but others added from the superposed parts of the brain.

In the higher mammals it was shown by von Gudden[2] that in the chiasma the majority of the fibres forming one optic nerve pass to the tract of the opposite side, but that a portion of the fibres remain in the tract of the same side.

This was inferred because removal of one optic bulb caused in young rabbits a degeneration in the associated optic nerve and also in *both* optic tracts—most marked, however, in the tract of the side opposite to the lesion.

[1] Onufrowicz: " Exper. Beitrag zur Kenntniss des centralen Ursprunges des Nervus acusticus," *Inaug. Diss.*, 1885.

[2] von Gudden : *Gesammelte und hinterlassene Abhandlungen*, Wiesbaden, 1889.

Conversely, the section of one optic tract causes a degeneration in both optic nerves, the nerve of the side opposite to the lesion being most affected, and a smaller degeneration appearing in the nerve of the same side (see Fig. 181).
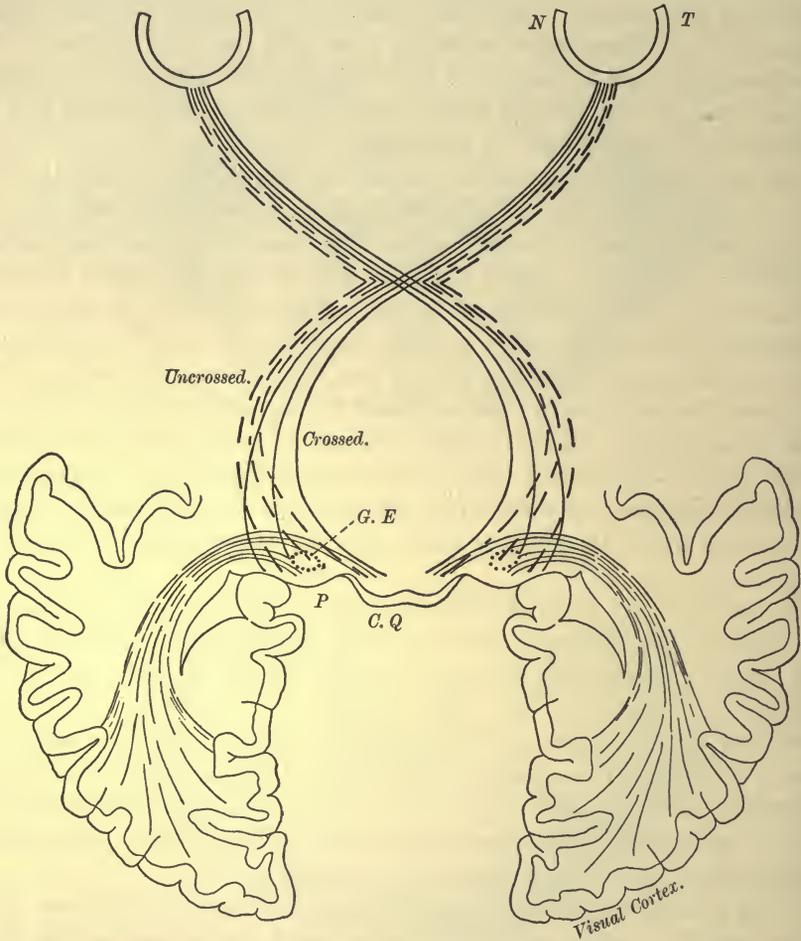
Fig. 181.—Illustrating the relations of the afferent fibres in the optic nerve. The crossed fibres are indicated by solid lines, the uncrossed fibres by broken lines: *N*, nasal side of the right eye; *T*, temporal side of the same ; *G. E*, geniculatum externum : *P*, pulvinar; *C. Q*, quadrigeminum anterius.

It appears from this that in the higher mammals an optic tract is composed of fibres from both optic nerves, but mainly of fibres from the nerve of the opposite side. In the fish, amphibia, reptiles, and birds—except the owls [1]— as well as in the lower mammals (mouse and guinea-pig, for example) the decussation appears to be complete.[2] For the partial decussation in the owls the evidence is physiological. This distribution of the optic fibres was asso-

[1] Ferrier: *The Croonian Lectures on Cerebral Localization*, London, 1890, p. 70.
[2] Singer und Münzer: *Denkschriften der math.-naturwiss. Classe der kais. Akademie der Wissenschaften*, 1888, Bd. lv.

ciated by von Gudden with the position of the eyes in the head. The extreme lateral position of the eyes as it occurs in the lower mammals permits of but little combination of the two visual fields; whereas the position in man, in a frontal plane, permits a combination of the fields to a much greater degree. It was in accordance with this principle that partial decussation of these nerves was anticipated by von Gudden in the owl, although the histological evidence for it was not obtained by him.

In man the evidence from degeneration in the optic nerve points to the presence of a crossed and an uncrossed bundle of fibres in each optic nerve, the uncrossed being much the smaller of the two bundles. The contrary view of complete decussation has been maintained by Michel.[1] The central ends of the afferent optic fibres forming an optic tract are distributed between the anterior quadrigeminum, the geniculatum externum, and the pulvinar of the same side. By central cells located in these latter structures the pathway is continued to the occipital cortex of the hemisphere of the same side, by the fibres passing in the occipital end of the internal capsule and forming the optic radiation. It must be remembered, however, that between the cortex and the primary centres, and again between these centres and the bulb, there are pathways conducting *from* the cortex to the primary centres, and also from the primary centres to the retina.[2]

As the result of partial decussation it will be seen that the relations of the two bulbs to the cortex is this: The nasal or crossed bundle of the contra-lateral bulb and the temporal or uncrossed bundle of the bulb of the same side come together in the optic tract of one side, and are associated with the occipital lobe of that side. Hence it would appear that hemianopsia or blindness in the corresponding halves of the two eyes following a lesion of the optic pathway anywhere behind the chiasma would be, in some measure, explained by this anatomical arrangement. If strictly interpreted an approximately equal number of fibres would be expected for each half of the retina. Such, however, has not been established as the relation between the areas of the bundles. It is to be added, nevertheless, that ana-tomical arrangements such as decussations are probably open to wide indi-vidual variations, and hence that many more observations are required before we can say what is the usual relation between these two bundles.

With a view to determining the exact location of the cortical centres in man many observations have been made. The cuneus and immediately sur-rounding parts of the cortex are those most concerned. Henschen[3] indicates the calcarine fissure and its immediate neighborhood as the most important locality. Observations on the arrest in the development of the cortex due to early blindness following destruction of the bulb in the case of the blind deaf-mute Laura Bridgman show the entire cuneus to be the central and funda-mental portion, while the associated portions extend some distance on to the

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[1] *Kölliker's Festschrift,* Würzburg, 1887.
[2] von Monakow : *Archiv f. Psychiatrie,* 1890, Bd. xx. H. 3.
[3] *Experimentelle und pathologische Untersuchungen über der Gehirn,* Upsala, 1890-92.

convex surface of the hemisphere.[1]   Ferrier[2] from the study of monkeys em-
phasizes the importance of the cortex of the angular gyrus; but these various
results must ultimately be harmonized through studies of degeneration in man
and the monkeys which will show the relative values of the several parts, all
of which are in some degree involved.

First Nerve.—Comparative anatomy indicates that the parts of the en-
cephalon mediating the sense of smell are most closely connected with the
cerebral hemispheres, in the sense that phylogenetically the first development
of the hemispheres was in connection with the central terminations of the
olfactory tracts.[3]   It happens in man, however, that although the cerebral hem-
ispheres are proportionately much more massive than in the lower mammals,
yet the olfactory bulbs and tracts are at the same time but poorly developed.
The pathway of the olfactory impulses is from the olfactory area in the nose
to the olfactory bulb of the same side, thence *via* the olfactory tract to its
termination in front of the anterior perforated space, one branch of the tract
passing directly into the substance of the gyrus fornicatus at this point, and
the other going into the more lateral portion represented in man by the tem-
poral end of the gyrus hippocampi.   The cortical areas, together with the
olfactory lobe and tract, form the rhinencephalon of the comparative anat-
omists.   It has been shown, nevertheless, by Hill[4] that in anosmic mammals
the fascia dentata alone varies with the development of the olfactory apparatus.
The experimental pathological evidence is very meagre in relation to these
nerves, but, on the other hand, the anatomical evidence is of the best.

The brief sketches of the pathways for incoming impulses indicate that
with the exception of those coming by the olfactory tract, they arrive ulti-
mately at the cerebral cortex over the fibres forming the internal capsule,
most, if not all, passing by way of the thalamus.   In the cerebral cortex are
found the terminal branches of the last cell-groups furnishing neurons which
conduct toward the cerebrum, and these are arranged in several layers corre-
sponding to the various strata of fibres which the cortex always shows.

F. Localization of Cell-groups in the Cerebral Cortex.

The foregoing section has brought to light the fact that groups of incom-
ing impulses find their way to the cerebral cortex.   The path to the cerebrum
is best developed in the higher animals.   In any case, the impulse in order to
produce evident responses must finally escape from the central system into the
tissues controlled, and using the reactions of the expressive tissues as a guide,
it is our present purpose to trace the impulses in those cases in which the cor-
tex forms part of the path.   We turn, therefore, to the study of those parts
of the cerebral cortex the direct stimulation of which produces impulses that
pass to cell-groups lying more or less caudad in the central system.

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[1] Donaldson: *American Journal of Psychology*, 1892, vol. iv. No. 4.
[2] *The Croonian Lectures on Cerebral Localization*, London, 1890.
[3] Sir William Turner: *Journal of Anatomy*, 1890; Edinger: *Anatomische Anzeiger*, 1893.
[4] *Philosophical Transactions of the Royal Society*, 1893, vol. clxxxiv.

Earlier Observations.—It was demonstrated by Fritsch and Hitzig in 1870[1] that if a constant current was applied to the surface of the dog's brain, it was possible by interrupting it to obtain movements of the limbs and face when the electrodes were placed on certain parts of the cerebral cortex, and the reaction varied according to the place of stimulation, a constant relation subsisting between the two. From this time on, active investigations of the relations thus suggested have been pursued, both by stimulating small areas in the cortex of various animals, including the monkey and man, and by the removal of various parts of the cerebral hemispheres and cortex, together with the study of the effects of pathological lesions in man. The results following removal of parts are complicated by the transitory effects of the lesion, and can best be treated by themselves later on. The results following the stimulation of the cortex are the simplest, and will next be described.

Stimulation of Cortex.—The common method of experiment is to apply the faradic current by means of fine but blunt electrodes, the ends of which are but two or three millimeters apart, to the exposed surface of the cerebral hemispheres, the pia being undisturbed. Rabbits, dogs, and monkeys have been the animals most commonly studied.

If the current be slight, its application for one or more seconds causes a response in the shape of movements of muscles, which are thrown into co-ordinated contraction. The contraction continues for some time after the stimulus has been removed. When the stimulus is very strong, instead of a limited and co-ordinated response, there may be a widespread contraction of many muscles, resembling an epileptic convulsion. This, however, occurs more commonly in the lower than in the higher mammals. On the other hand, the irritability of the cortex is easily reduced, so that it becomes irresponsive, and often immediately after the first exposure of the brain there is a time during which a response cannot be obtained.

Turning to the areas of the cortex which are occupied by the extension of
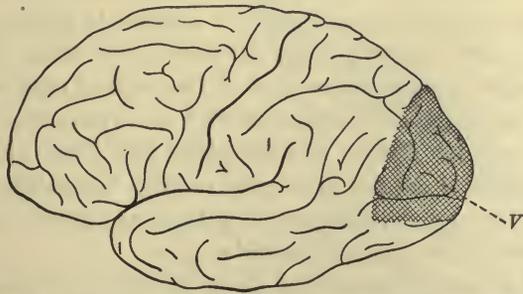
Fig. 182.—Lateral view of a human hemisphere. The cortical visual area on this aspect is shaded (*V*).

the pathways from the special sense-organs, it is found that the visual area alone exhibits any elaboration when examined by the method of stimulation.

[1] *Archiv für Anatomie und Physiologie,* 1870.

To be sure, Ferrier[1] very early pointed out that stimulation of the other sensory areas causes movements. It was by means of the movements thus obtained that he sought to localize the sensory centres, assuming that the movements were in response to sensations caused by the irritation of the cortex.

As the result of stimulation of a sensory area the muscles of the sense organ itself or those immediately associated with it respond (see Figs. 182, 183).
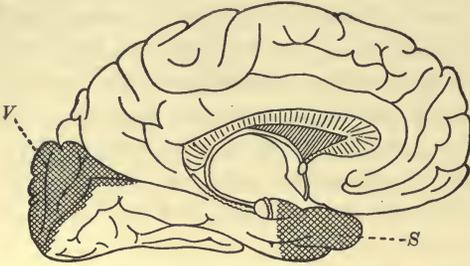
Fig. 183.—Mesial view of a human hemisphere. The cortical visual area is shaded, *V;* cortical area for smell, *S.*

Shäfer[2] has shown in the monkey that the dorsal portion of the visual area is associated with the upper portion of the retina, the eye being turned downward as the result of stimulating this portion. This is interpreted as a movement of the eye intended to bring a stimulus falling on the upper part of the retina into the centre of the field of vision. When the stimulus is applied to the ventral portion of the area a corresponding upward movement of the eye occurs, and the corresponding relation holds for the stimulation of the lateral and mesial portions of the area. These movements occur in both eyes, although the stimulus is applied to one lobe only, and hence the two retinal fields appear to be superposed in the visual cortex of each hemisphere.

The experiments on the stimulation of the other sensory areas show, in the first place, that these areas contain cells the stimulation of which causes the contraction of certain muscles immediately associated with the organ of sense, and, in the second place, that while each of the areas is pre-eminently concerned with the reception of impulses from a particular sense-organ, yet no one of them is exclusively sensory.

Deferring for a moment the other evidence by which the sensory characters have been established, and also the arrangements within the cortex by which any group of muscles can be made to respond to stimuli arriving at any sensory area, we shall follow out the distribution of those cortical cells the stimulation of which causes contractions of the skeletal muscles.

The results here presented were obtained from the electrical stimulation of the monkey's brain by Beevor and Horsley[3] (see Figs. 184, 185). These experimenters explored the exposed surface of the hemisphere with the electrodes, moving them two millimeters at a time, and at each point noting the muscle-group first thrown into contraction.

As the result of many observations on the monkey, it is possible to map out the cerebral cortex in the following way: The surface of the hemispheres is divided into regions (motor and sensory regions), which are the largest sub-

[1] *The Functions of the Brain,* 1876.
[2] *Proceedings of the Royal Society,* London, 1888, vol. xliii.
[3] *Philosophical Transactions of the Royal Society,* 1888–90.
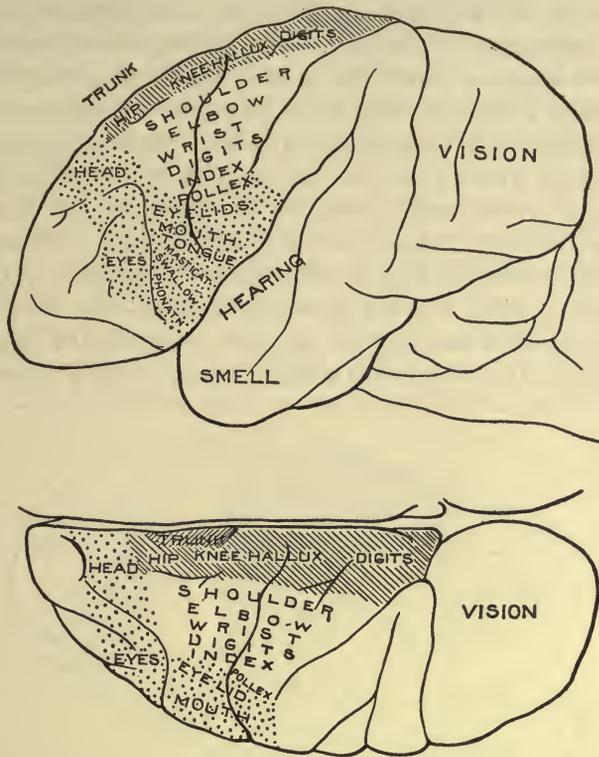
FIG. 184.—Brain of the macaque monkey, showing the sensory and motor areas. In the sensory region the name of the sensation is over the locality most closely associated with the corresponding sense-organ; in the motor region the name of the part is written over the portion of the cortex which controls it. The upper figure gives a lateral view of the hemisphere, and the lower a dorsal view (Beevor and Horsley).

divisions. These are subdivided into areas for the muscle-groups belonging to different members of the body—arms, head, trunk, etc., or those areas
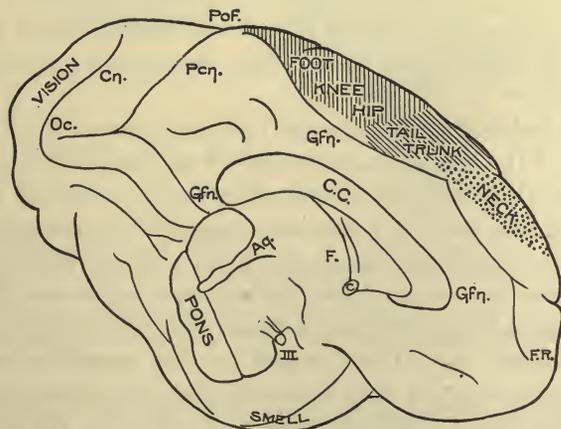
FIG. 185.—Mesial surface of the brain (monkey). The localization of motor functions is indicated along the shaded portion of the marginal gyrus. The location of the visual area is indicated at the tip of the occipital lobe, and the location of the olfactory area at the tip of the temporal (Horsley).

within which all the impulses from a given sense-organ reach the cortex. The areas in turn may be marked off into centres, formed by the groups of cells which, for example, control the smaller masses of muscle belonging to a given segment of a limb, or in the visual area are represented by those cells especially connected with one part of the retina. There is thus a motor region the stimulation of which gives rise to the more evident bodily movements. Within this are several subdivisions, the stimulation of one of which is followed by movements of groups of muscles—for instance, those controlling the arm—and within such an area in turn come the smaller centres, or those the stimulation of which is first followed by movements at one joint only.

Another method of studying the cortex is to regard the character of the movement obtained by stimulating a single area, as that of the arm. Figure

FIG. 186.—Showing in the arm-area (monkey's brain) the localization of movements having different characters (after Horsley).

186 shows that stimulation of the upper arm-area gives rise in the first instance to movements of extension, whereas the lower arm-area yields those of flexion. This basis of subdivision is, however, not so useful as the analysis into centres. As the smallest subdivisions, the centres are most convenient for further study.

If a vertical incision be carried around such a centre so as to isolate it from the other parts of the cortex, the characteristic reactions still follow the stimulation of it, indicating that the special effect can be produced by the passage of impulses from the point of stimulation toward the infracortical structures. If, in addition, a cut be made below the cortex and parallel with its surface, then stimulation of the cortex above this section is ineffective, thus indicating that the impulses pass from the cortex directly into the substance of the hemisphere along certain nerve-tracts, which by this operation were sectioned. Further, if the bit of cortex thus separated from the underlying white substance be removed and the faradic current be applied to the white substance beneath, a reaction of the same type and involving the same muscles can be obtained, although it differs from that to be gotten from the cortex itself, in

the first place by being less co-ordinated, in the second by continuing only so long as the stimulus lasts, and in the third place by giving rise to less intense electrical changes connected with the passing impulse.

These facts, taken together, lead to the conclusion that when the cortex is stimulated the impulses concerned in producing the muscular contractions traverse cell-bodies at the point of stimulation, and are transmitted thence through the underlying fibres. We shall see later that this direct course probably does not represent the sole pathway for these impulses.

Secondary Degeneration.—The course of these impulses is next inferred from the relation between the removal of different parts of the cortex and the consequent secondary degenerations throughout the length of the central nervous system. When the part of the cortex removed is taken from the motor area, then the degeneration occurs in the internal capsule and in the
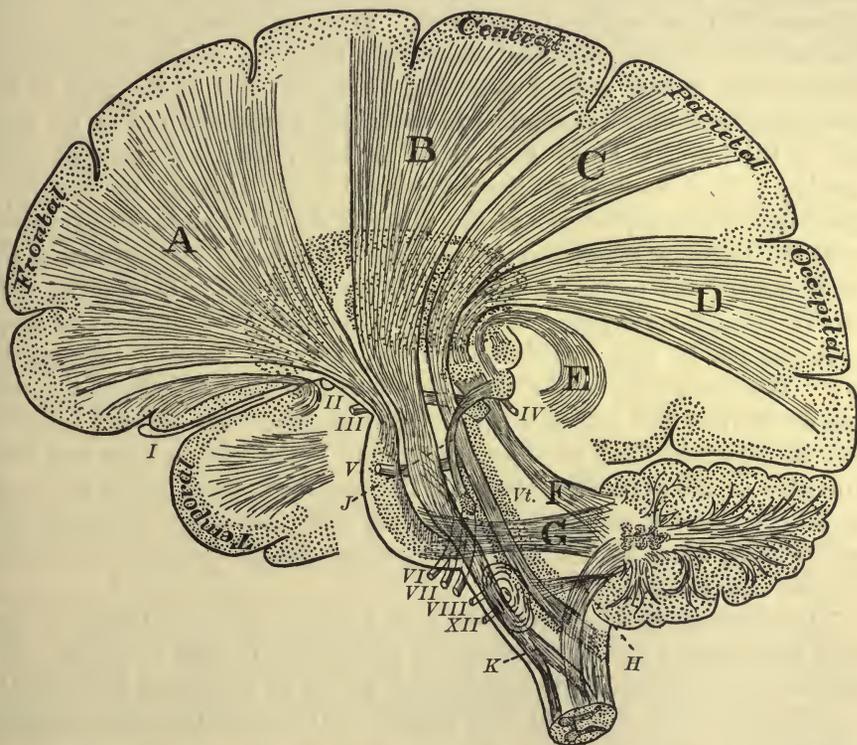
FIG. 187.—Schema of the projection fibres within the brain (Starr); lateral view of the internal capsule: *A*, tract from the frontal gyri to the pons nuclei, and so to the cerebellum; *B*, motor tract; *C*, sensory tract for touch (separated from *B* for the sake of clearness in the schema); *D*, visual tract; *E*, auditory tract; *F, G, H*, superior, middle, and inferior cerebellar peduncles; *J*, fibres between the auditory nucleus and the inferior quadrigeminal body; *K*, motor decussation in the bulb; *Vt*, fourth ventricle. The numerals refer to the cranial nerves. The sensory radiations are seen to be massed toward the occipital end of the hemisphere.

callosum. The path of the fibres forming outgrowths of the cortical cells can be followed thence through the crusta and pyramids to the spinal cord.

After removal of the motor region of one cerebral hemisphere the degen-

eration is mainly in the internal capsule and crusta of the same side, though by way of fibres crossing in the callosum it may be traced on the other side also. At the decussation of the pyramids the fibres occupying the internal capsule of the same side as the lesion, for the most part cross the middle line (see Fig. 187). The portion which remains uncrossed passes as the direct pyramidal tract of the ventral columns in man, while the crossed bundle, which is much the larger, lies in the dorso-lateral field of the lateral column, forming the crossed pyramidal tract. This, however, is only the principal, but not the complete, distribution of the degenerated fibres.

The direct pyramidal tracts disappear in the cervical region, having entered the substance of the cord by way of the ventral commissure, and probably having there undergone decussation. The crossed pyramidal tract shows the greatest diminution in area after passing caudad of the cervical and lumbar enlargements, and hence it is inferred that the pyramidal fibres largely terminate in these regions of the cord. Most important, however, is the observation of Sherrington,[1] that even with a unilateral cortical lesion degeneration occurs in *both* crossed pyramidal tracts, and that at the level of the two enlargements the degenerations in the crossed pyramidal tract on the *same* side as the lesion is larger than above or below these enlargements, thus showing a local increase in the degenerated fibres running on this side. Sherrington's first explanation of this bilateral degeneration in the pyramidal tracts was based on the assumption that fibres which had once crossed at the decussation of the pyramids recrossed at lower levels. If, however, such were the case, the recrossing would carry a number of the degenerated fibres across the middle line, and decrease by so many the fibres in the opposite half. The diminution of the fibres in number on the first side of the cord does not warrant this inference: Sherrington therefore put forward the view that the pyramidal fibres recrossing in the cord are derived in large part from a division of the pyramidal fibres into two branches, one of which may cross to the opposite side of the cord, while the other continues its first course; such dividing fibres he designates as "geminal fibres," the number of which is by no means small.

The observations of Sherrington were made on monkeys (Macacus) and dogs, and probably the arrangements of these fibres in man is similar. The observations are particularly significant as giving an anatomical basis for the control of the movements in both halves of the body from each cerebral hemisphere.

The continuous degeneration, coupled with the histological evidence for the absence of intervening nerve-cells, indicates that the cell-bodies in the cortex have neurons that extend all the way to the cell-groups of the spinal cord, even as far as the sacral region. The neurons of one group of these cortical cells pass, however, to the cell-groups in the cervical enlargement, while those from others pass to the groups in the lumbar enlargement. It thus happens that if the spinal cord be cut across in the middle of the thoracic region, and

[1] *Journal of Physiology*, 1889, vol. x.

then the leg-area (see Fig. 153) be stimulated, an electrometer applied to the cut end of the cord will show the passage of nerve impulses, because the electrometer is applied to a tract of fibres on their way to the lumbar enlargement, and the fibres originate in cortical cells within the region stimulated. When, however, the cortical stimulus is made in the arm-area, the electrometer being applied as before, no electric change occurs, for the neurons of the cells in the arm terminate in the part of the cord containing the cell-groups which control the muscles of the arm, and these all lie cephalad to the point of section of the cord. It is evident, therefore, that the arrangement is a comparatively simple one—namely, an extension of the neurons of the several groups of cortical cells from the different areas for the leg, arm, face, etc., to the axial cell-groups which control the muscles of these parts, and which are situated in the cord. Sherrington reports[1] a degeneration of some fibres as far as the lumbar enlargement even when the lesion is confined to the cortical area for the arm. Assuming the correctness of this observation, it is to be harmonized with the preceding statements to the effect that stimulation of the arm-area does not produce an electrical variation in an electrometer applied to the crossed pyramidal tracts in the mid-thoracic region by the fact that the number of these long fibres is small.

The cortical cells in the motor region belong to the group of central cells —*i. e.* their neurons never leave the central system—and hence they are engaged in distributing impulses within it. To the axial cell-groups in the cord they bring impulses, and therefore from the standpoint of these latter may be considered as afferent, whereas, owing to the fact that they carry impulses away from the cortex, they are sometimes called efferent. Confusion can be avoided, however, by refraining from either term. Just how these two sets, the cortical and the cord elements, are related still requires to be worked out. The number of fibres in the pyramidal tracts indicates that there certainly is not one fibre for each cell in the axial cell-groups, because the number of pyramidal fibres is very much less than is the number of cells which they control. This discrepancy is in some measure relieved by the formation of "geminal" fibres already described. Moreover, the branching of the pyramidal fibres near their termination is very probable, and the most plausible view at present is that each pyramidal fibre by means of its collaterals comes into physiological connection with a considerable number of efferent cells, and probably the cells controlled by any one fibre at its terminus form more or less compact groups.

Mapping of the Cortex.—Having sketched the relations of the pyramidal cells forming the motor region of the cerebral cortex to the parts lying below, it will be important to study the arrangement, size, subdivisions, and comparative anatomy of this region, and then to examine the relation of it to the other parts of the cortex. The observations here quoted are those on the monkey only.

On glancing at Figure 184 it is evident, first, that the areas for the head

[1] *Journal of Physiology*, 1869, vol. x.
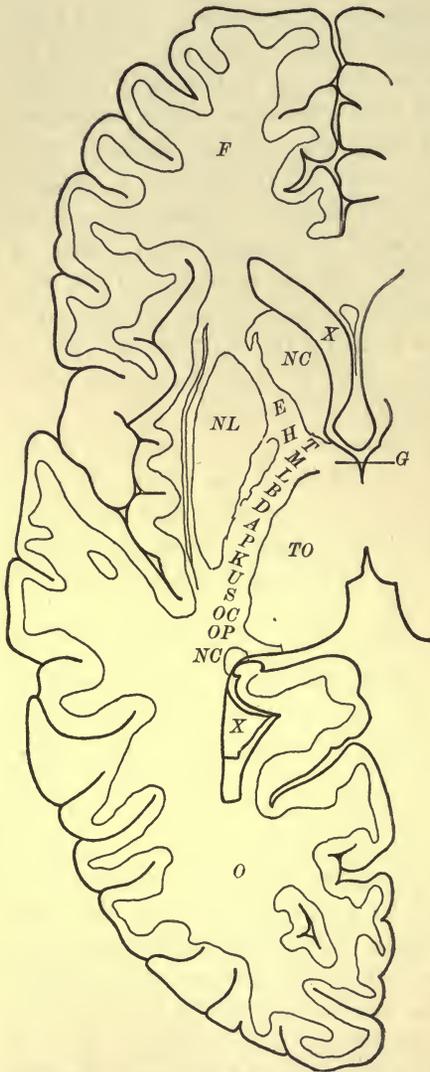
Fig. 188.—Horizontal section of the human cerebrum, showing the internal capsule on the left side: *F*, frontal region; *G*, knee of the capsule; *NC, NC*, caudate nucleus; *NL*, lenticular nucleus; *O*, occipital lobe; *TO*, thalamus; *X, X*, lateral ventricle. In the internal capsule the letters indicate the probable position of the bundles of fibres which upon stimulation give rise to movements of the parts named or which convey special sets of incoming impulses; *E*, eyes; *H*, head; *T*, tongue; *M*, mouth; *L*, shoulder; *B*, elbow; *D*, digits; *A*, abdomen; *P*, hip; *K*, knee; *U*, toes; *S*, temporo-occipital tract; *OC*, fibres to the occipital lobe; *OP*, optic radiation (based on Horsley).

and face are widely separated from each other—that the arm-area lies between them, and that the area for the trunk, though less schematically placed, is located between the arm and leg. This arrangement is more typically represented on the mesial (Fig. 185) than on the convex surface of the hemisphere.

The muscle-groups when enumerated cephalo-caudad being those for the head, arm, trunk, and legs, the serial order of the cortical areas is thus in correspondence with the order of the muscle-groups which they control.

The Size of the Cortical Areas.—Evidently there is no direct relation between the extent of a cortical area and the mass of muscles which it controls; certainly in man the mass of muscles in the leg is five times greater than that in the arm, and this many times greater than that in the face and head; yet it is for the last area that the greatest cortical extension is found. Mass of muscle and extent of cortical area do not therefore go together.

When the movements effected by the muscles in these several areas are considered, we find that such movements become more complex and more accurate as we approach the head, and it therefore accords with the facts to consider the extension of the motor areas as correlated with the refinement of the movements which they control—a relation which may be expressed anatomically as an increase in the number of cortical cells controlling the related cell-groups in the cord.

Subdivision of Areas.—The areas which have been described are further subdivided, the subdivisions in the arm-area being the clearest. Here it is found that the stimulation of the upper part of the arm-area gives rise to movements which start at the shoulder,

while stimulation at the lower part of this area gives rise to movements first involving the fingers, and especially the thumb. The centres from which these several reactions may be obtained occupy, as Figure 184 shows, narrow fields across the cortex in a fronto-occipital direction. Moreover, the centre for the most proximal joint of the arm is farthest removed from that for the most distal, while the intermediate joints are represented by their several centres lying in regular order between these two. A similar arrangement appears in the subdivisions of the leg, and in the face-area as well.

Interpreting these facts in the terms of nerve-cells and their arrangement, it appears that in the shoulder centre the neurons of the cortical cells that discharge downward pass predominantly to the efferent cell-groups which in the spinal cord directly control the muscles of the shoulder, and that a similar arrangement obtains for the other centres in this region with the corresponding cell-groups in the cord. The stimulation of the different portions of the internal capsule where it is composed of bundles of fibres coming from the motor region shows (observations on orang-utang) that the fibres running to the several lower centres are here aggregated, and are ranged in the same order as the cortical centres themselves (see Fig. 188).

Separateness of Areas and Centres.—As we ascend in the mammalian series there is an increase in the perfection with which cells forming the several centres are segregated, though the areas in the different forms tend to hold the same relative positions.[1]

Figures 189, 190 give the localizations recently obtained in the rabbit's brain by stimulation (Mann). The various areas occupy a large proportion of the cortex, and in some cases come very close together, so that they are not easily separated by experiment.
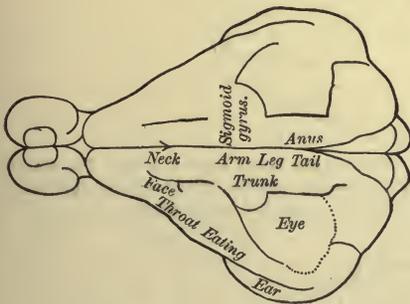
FIG. 189.—Rabbit's brain, dorsal view. The areas indicated are those the stimulation of which causes a movement of the parts named (Mann).
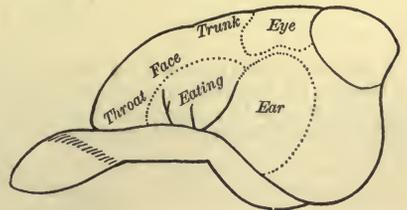
FIG. 190.—Rabbit's brain, lateral view. The areas indicated are those the stimulation of which causes a movement of the parts named (Mann).

In the lower monkeys (*Macacus sinicus*) these cell-groups are segregated, so that those associated with the cervical portion of the cord and forming the arm-area are much more together, and quite separate from those associated with the lumbar region, leg-area. In the orang-utang,[2] and to a greater extent in man, a further separation occurs, so that they come to be surrounded

[1] Mann: *Journal of Anatomy and Physiology*, 1895, vol. xxx.

[2] Beevor and Horsley: *Proceedings of the Royal Society of London*, 1890–91, vol. xlviii.
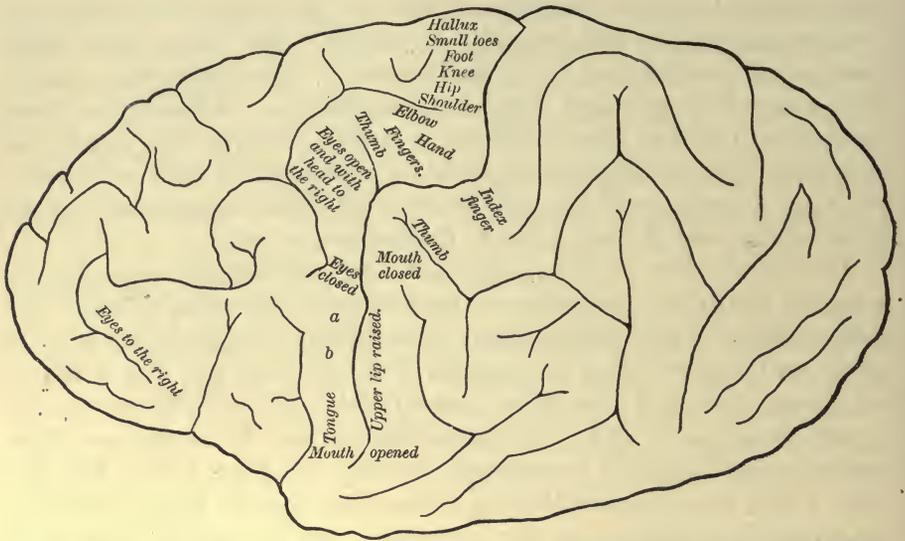
Fig. 191.—Lateral view of the left hemisphere of an orang-utang, showing the motor area about the central fissure (Beevor and Horsley).

by parts of the cortex from which no response can be obtained upon direct stimulation (see Fig. 191).
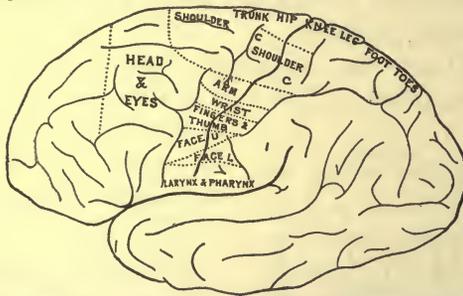
Fig. 192.—Lateral view of a left human hemisphere, showing the motor areas in man. The schema is based on the observations on the monkey, on pathological records, human, and on direct experiments on man. It is to be remembered that in the human brain the excitable localities are surrounded by rather extensive areas not directly excitable (Dana).
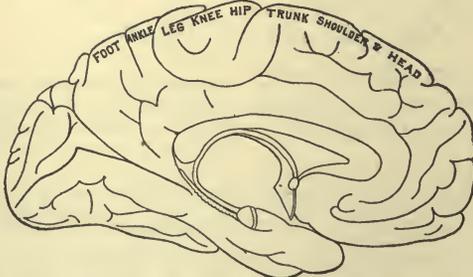
Fig. 193.—Mesial view of a human hemisphere, showing motor areas. Formed in the same way as Figure 192.

By a few direct experiments and by many pathological observations something is known of the motor centres in the human cerebral cortex. When

the results are plotted they give a distribution such as is shown in Figure 192. At the same time all such figures are largely compiled from results obtained on the monkey. It is here seen that the two central gyri are the principal seat of these areas, and that it is only along the great longitudinal fissure dividing the hemispheres that the motor areas extend beyond this limit in a cephalo-caudad direction. Perhaps the relation most worthy of remark is the comparatively small fraction of the cortex concerned with the direct control of the spinal cord cells. The motor areas in man are elaborated, not so much by the increase in the number of the cells controlling the lower centres, as by an increase in the number of those cells under the influence of which these areas react. The relation of the areas in a frontal section is shown in Figure 194.
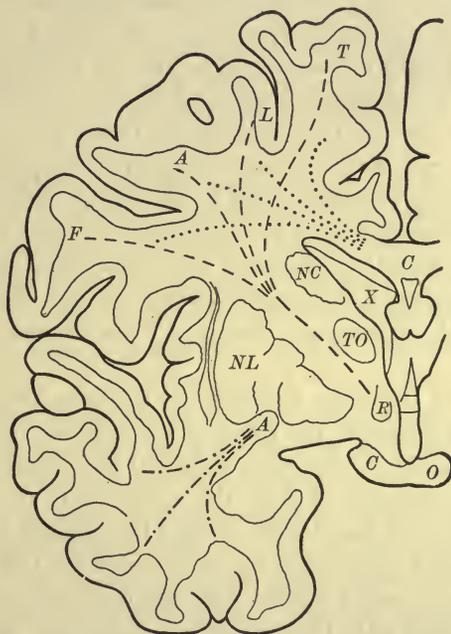
Fig. 194.—Frontal section of the human cerebrum on the left side. The fibres forming the internal capsule (— — —), the callosum (· · · · ·), and the anterior commissure (· — · — · — · —) have been indicated. *T*, cortical area for the trunk; *L*, cortical area for the leg; *A*, cortical area for the arm; *F*, cortical area for the face; *A*, anterior commissure; *C*, callosum; *CO*, optic chiasma; *NC*, caudate nucleus; *NL*, lenticular nucleus; *R*, fornix; *TO*, thalamus; *X*, lateral ventricle.

Sensory and Motor Regions.—If an attempt is made to unify the construction of the entire cortex by bringing the motor and sensory areas under a common law, it must be based on the fact that the system of neurons bringing impulses *to* the motor region forms part of the afferent pathways from the skin and muscles. To Munk[1] is due the credit of having from the first looked upon the responsive cortex as marked off into areas within which certain groups of afferent fibres terminated, so that apart from the sensory areas named from the special senses, he calls the area which controls the skeletal muscles the "Fuhlsphäre," on the assumption that in it end the fibres bringing in impulses

[1] *Ueber der Functionen der Grosshirnrinde*, 1881.

from the skin and muscles. It has been suggested, to be sure, that separate localities were the seat for the dermal and muscular sensations. Ferrier[1] indicated the limbic lobe, especially the hippocampal gyrus, while Horsley and Schäfer[2] argued for the gyrus fornicatus. At present the weight of evidence is in favor of the location of the centres for dermal and muscular sensations in the same area as that from which the muscles of the trunk and limbs can be made to contract.[3] Both in monkeys and in man defects in sensation are not permanent after limited lesions of the cortex, but, as suggested by Mott, the wide distribution of the incoming impulses would explain this result.

Thus the entire portion of the cortex to which a definite function can be assigned must be looked upon as made up of fibres which bring impulses into it and cell-bodies which by their discharge send impulses to other divisions of the central system as well as to other parts of the cortex itself. All parts of the cortex having assigned functions give rise on stimulation to movements, but in the case of the movements aroused by the stimulation of the sensory areas, so called, they involve the contractions of only those muscles controlling the external sense-organ, as the eyeball, external ear, tongue, and nostrils, and, though physiologically important, and in the case of the eye at least reaching a high degree of refinement, they are quantitatively very insignificant as compared with the responses to be obtained from stimulating the "motor region," from which contractions of the larger skeletal muscles are obtained. Hence the significance of the usual terms "sensory" and "motor" in describing the respective regions.

Multiple Control from the Cortex.—It has been found that stimulation of the cortex in the region of the frontal lobes marked "eye" (Fig. 184) was followed by movements of the eye. Schäfer[4] has shown that very precise movements of the eye also follow the stimulation of the temporal and various parts of the occipital cortex. Since the efferent fibres which control the muscles concerned start from the cell-groups of the third, fourth, and sixth cranial nerves, it would appear most probable that in both parts of the cortex there are located cells the neurons of which pass to those groups and are capable of exciting them. An alternative hypothesis—namely, that the impulses which produced the movements when the occipital region was stimulated, travelled first to the cortical cells in the frontal lobe and thence by way of them to the efferent cell-groups—was at one time considered, for the latent period of contraction of these muscles was less by several hundredths of a second when the stimulus was applied in the frontal region than when applied elsewhere. The experiments of Schäfer show, however, that when the occipital and frontal lobes are separated from one another by a section severing all the association fibres, still the reactions can be obtained by stimulation in the former locality,—showing that the connections of the two

[1] *The Functions of the Brain,* 1876.

[2] *Philosophical Transactions of the Royal Society,* 1888, vol. cxxix.

[3] Mott : *Journal of Physiology,* 1894, vol. xv.

[4] *Proceedings of the Royal Society,* 1888, vol. xliii.

cortical areas with the cell-groups controlling the muscles of the eye are independent of each other.

This instance of the direct control of the same axial cell-groups from different areas of the cortex is analogous to the control of efferent cell-groups in the spinal cord, either by impulses coming down from the cerebrum or by those entering the cord directly through the dorsal roots, and the instance here cited is typical of a general arrangement.

Cortical Control Crossed.—Where the stimulation of the cerebral cortex causes a response on one side only, that response is on the side opposite to the stimulated hemisphere. It sometimes happens, however, that two groups of symmetrically placed muscles both respond to the stimulus applied to one hemisphere only, but these cases:—the conjugate movements of the eyes; movements of the jaw muscles or those of the larynx,—always depend on the response of muscles which are naturally contracted together.

This reaction depends on the arrangement of the fibres in the cord, since in lower mammals (dog and rabbit, for example) it is not seriously disturbed by the removal of one hemisphere.

Course of Impulses Leaving the Cortex.—In the higher mammals, as well as in man, it is by way of the pyramidal fibres that impulses travel from the cortex to the cell-groups of the axis. The pyramidal tracts by definition form in part of their course the bundles of fibres lying on the ventral aspect of the bulb, caudad to the pons, ventrad to the trapezium, and between the olivary bodies. According to Spitzka,[1] these are absent in the case of the elephant and porpoise. It has been pointed out, too, that removal of a hemisphere causes in the dog and most rodents a degeneration of other parts of the cord (dorsal columns) than those occupied by the pyramidal tracts in man.[2] The fibres passing from the cortex to the efferent cell-groups in the cord do not, therefore, hold exactly the same position in various mammals.

Size of Pyramidal Tracts.—It has been clearly shown that if the cross sections of the cords of the dog, monkey, and man be drawn of the same size, the pyramidal fibres being indicated, then the area of this bundle is proportionately greatest in man and least in the dog, the monkey being intermediate in this respect. The relations thus indicated are evident—namely, that the number of fibres controlling the cell-groups in man is the largest, and is much larger than that in the lower animals.

The relative areas of the pyramidal tract, the area of the entire cord being taken as 100 per cent. at corresponding levels, are given by v. Lenhossek[3] for the following animals:

Mouse	1.14 per cent.
Guinea-pig	3.0 "
Rabbit	5.3 "
Cat	7.76 "
Man	11.87 "

[1] *Journal of Comparative Medicine and Surgery*, 1886, vol. vii.

[2] von Lenhossek: *Anatomischer Anzeiger*, 1889.

[3] *Die feiner Bau des Nervensystems im Lichte neuester Forschungen*, Basel, 1893.

This relation is to be carefully noted, for with it is correlated the degree of the disturbances in the reactions of the entire nervous system following removal of parts of the encephalon, the effect being slight when the encephalon is connected with the cord by a small number of fibres, and serious when the connection is by many fibres, as in the case of man and the highest mammals.

G. Pathways within the Hemispheres.

If the guiding idea of the pathway of the nervous impulse through the central system had been rigidly followed, the association tracts in the cerebral hemispheres would have come up for discussion immediately after the description of the afferent pathways. The knowledge of the arrangement in the cerebral cortex which has been obtained from the stimulation of it is, however, so much less complicated than that obtained by other methods of investigation that the observations on this head were made introductory to the whole matter of localization, although in so doing the strict sequence of the presentation was interrupted and the emphasis put on the cell-groups which discharge from the cortex to the lower centres.

Determination of Sensory Areas.—The determination of the sensory areas in man has been through the study of brains modified by destructive lesions or congenital defects.

The cortical centre for smell, inferred from comparative anatomy and physiology to be at the tip of the temporal lobe and closely connected with the hippocampal gyrus and the uncus, has been similarly located in man on the basis of pathological observations; but the evidence is indirect and incomplete (see Fig. 195). Concerning the location of taste sensations even less is known. Both of these senses, it must be remembered, are insignificant in man, and hence their central locations have not been studied with great care.

Fig. 195.—Lateral view of a human hemisphere. The cortical area for smell is shaded (*S*); the cortical area for hearing is shaded (*H*).

On the other hand, the cortical areas for hearing and sight have been located with much more precision and certainty.

Damage to the first and second temporal gyri in man causes deafness in the opposite ear, and concordantly conditions of the ear which early in life lead to deafness and deaf-mutism are accompanied by a lack of development in these gyri.[1] Destruction of these temporal gyri on one side always causes deafness in the opposite ear, but there has not yet been reported a case of complete deafness due to a double cortical lesion alone.

[1] Donaldson: *American Journal of Psychology*, 1891.

In the case of the visual areas in man there is the same sort of evidence, but somewhat more exact. The destruction of the area represented by the cuneus and the surrounding cortex (see Figures 182 and 183) always injures vision, and the failure of the eyes to grow arrests the development of this portion of the hemisphere.[1]

Hemianopsia.—It is found, moreover, that injury to the visual area in one hemisphere produces usually a hemianopsia or partial defect of vision in both retinas. The homonymous halves are affected on the same side as the lesion, and the dividing line is usually vertical. The clinical picture corresponds to a semi-decussation of the optic tract and the representation of the homonymous halves of each retina in both hemispheres. At the same time the relation is much more complicated than at first sight appears, for the point of most acute vision is often unaffected in such cases ; and for this peculiarity we have no anatomical explanation.[2]

In neither vision nor hearing do we find in man any subcortical cell-groups capable of acting as centres ; that is, after the removal of the appropriate cortical region the corresponding sensations and reactions to the stimuli which arouse these sensations are completely and permanently lost.

From these facts, therefore, it appears that the impulses which give rise to visual and auditory sensations are delivered in certain parts of the cerebral cortex, and unless they arrive there the appropriate sensations are absent.

Association Fibres.—Common experience shows us that we can voluntarily contract any group of muscles in response to any form of stimulus— dermal, gustatory, olfactory, auditory, or visual. When, therefore, the hand is extended in response to a visual stimulus, the nerve-impulses pass first to the visual region, and then are transferred to the cortical cells controlling the muscles of the hand. This connection is accomplished through the so-called association fibres of the cortex. These fibres are formally described as those which put into connection different parts of one lateral half of any subdivision of the central system (see Fig. 196).

The bundles which are thus shown in the cerebral hemisphere must be looked upon as typical of the arrangement throughout the entire cortex, and, further, the arrangement in the cortex is typical of that in other parts of the central system. Anatomy would suggest, and pathology bears out the suggestion, that it is by these tracts that the impulses travel from one area to another.

Aphasia.—The development of the ideas bearing on this subject has been slow. After the publication of the great work of Gall and Spurzheim (1810–19) on the brain, some pathologists (Bouillaud, 1825 ; Dax, 1836), especially in France, were in search of evidence touching the doctrine of the localization of function. At the same time the subject of phrenology, as put forward by Gall and Spurzheim, was not in good repute, and anything which looked that way, even in a slight degree, was generally scouted. Broca, however, pub-

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[1] Donaldson: *American Journal of Psychology*, 1892, vol. iv.

[2] Noyes: *New York Medical Record*, 1891.

lished (1861) the important observation that when the most ventral or the third frontal convolution in the left hemisphere (often designated Broca's convolution) was thrown out of function, the power of expression by spoken words was lost, and hence the name of "speech-centre" has been applied to this convolution.

Since this discovery, which links the neurology of the first part of the
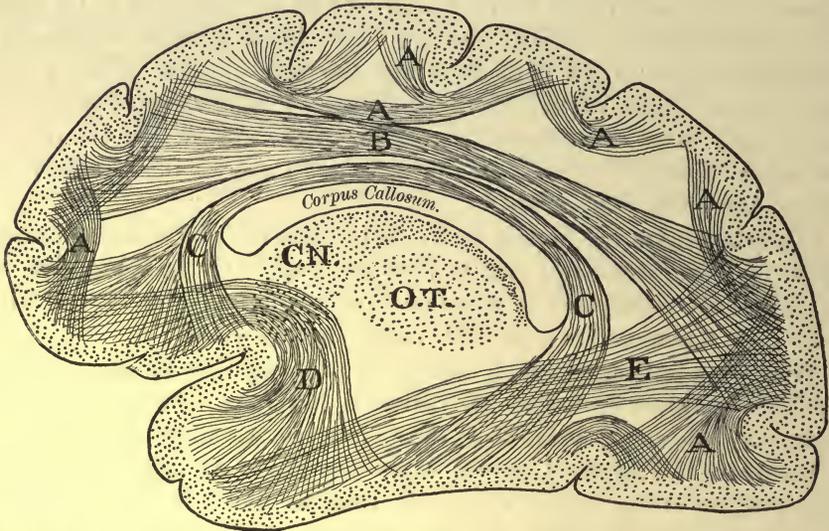
Fig. 196.—Lateral view of a human hemisphere, showing the bundles of association fibres (Starr): *A, A,* between adjacent gyri; *B,* between frontal and occipital areas; *C,* between frontal and temporal areas, cingulum; *D,* between frontal and temporal areas, fasciculus uncinatus; *E,* between occipital and temporal areas, fasciculus longitudinalis inferior; *C, N,* caudate nucleus; *O, T,* optic thalamus.

century with that of to-day, and also forms a fundamental observation in the modern doctrine of cerebral physiology, many steps have been taken.

It was early observed that although in such cases the capacity for spoken language was lost, nevertheless the muscles which were used in the act of phonation were by no means paralyzed. This relation is due probably to the fact that the speech-centre of Broca does not contain cells which connect directly with the lower nuclei controlling the muscles of phonation.

The interesting observation was also made that in the ordinary person the muscles could not be controlled for phonation from the right hemisphere. Thus the symmetrical portion of the right hemisphere has not the same physiological value.

Besides this lesion, which involves the cortex frontad to the motor region proper, numerous other lesions—namely, those which involve the tracts running between the areas of special sensation (vision and hearing, for example), and the motor or expressive region—produce corresponding results (see Fig. 197).

An individual in whom the association tracts between the visual and motor areas have been interrupted can, for instance, see an object presented to him in

the sense that he gets a visual impression, but because of the interruption of the association fibres the object is not recognized, and the impulses reaching this sensory area elicit no response from the muscles, the motor areas for which are located elsewhere.

Of these connections between sensory and motor areas a sufficient number have been studied to suggest that the typical arrangement of the cells in the cerebral cortex is the following: The afferent impulses are distributed in the sensory cortical areas among several classes of cells. Some of these, through their neurons, form association tracts by which the impulses are transferred from the sensory to the motor regions. Concerning
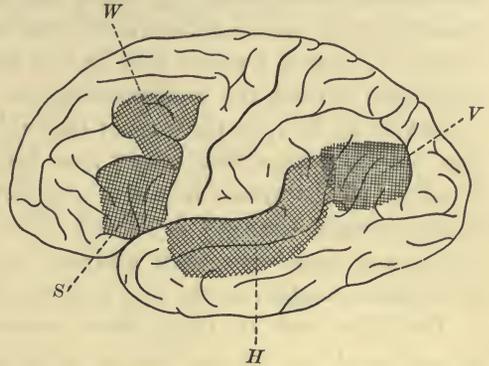
FIG. 197.—Lateral view of a human hemisphere; cortical area *V*, damage to which produces "mind-blindness;" cortical area *H*, damage to which produces "mind-deafness;" cortical area *S*, damage to which causes the loss of audible speech; cortical area *W*, damage to which abolishes the power of writing.

the exact manner in which the impulses arrive at these associating cells, or concerning the layer in the cortex which represents them, information is meagre, but the observations on the distribution of the fibres in the cortex suggest that the short association tracts must be at the level of the superficial fibre-layers, while the longer tracts extend far below the cortex, and would most naturally be associated with the deepest layers of cells.[1] Upon attempting to carry out this arrangement to anything like the completeness demanded by the physiological reactions, it is necessary to postulate the existence of such pathways between each sensory and each motor area, and thus there must be a pathway extending from every sensory to every motor area. This arrangement is of course to be pictured as modified in several ways.

In the first place, the connection between a given motor and a given sensory area is by no means proportionate in the several instances. The connection, for example, between the visual area and the motor area for the arm is probably represented by more nerve-elements, and these better organized, than the connection between the gustatory area and that for the movements of the leg.

When, therefore, it is said that such connections exist, it must be added always that the nexus is different for the several regions concerned, and, what is more, that in man, at least, it is different for the two hemispheres.

The Relative Functions of the Two Hemispheres.—When the subject is right-handed, it appears that in man injury to the left cerebral hemisphere is more productive of disturbance than injury to the right hemisphere. At the same time, lesion of the left hemisphere is far more frequent than that of

[1] Andriezen: *Brain*, 1894.

the right. So far as can be judged from experiments on man, the higher sense-organs, the eye and the ear, are more perfect, physiologically, on the right side. Since the connection of the sense-organs is largely with the cortex of the contralateral hemisphere, this means that the impulses going mainly to the left hemisphere are better differentiated than those going to the right. For these impulses to reach a motor area in the same hemisphere would appear to be easier than to reach the corresponding area on the opposite side, and it is thus possible to see how, on the basis of the slightly better sense-organs of the right side, the left-brained man might have been developed. The observations of Flechsig[1] on the pyramidal tracts also show that this tract, before medullation at least, may be unevenly developed on two sides of the cord, and the ease of control may thus be rendered unequal—a condition which must be dominant in the determination of the side of the body which shall be exercised.

Doubtless there are other factors concerned, and, moreover, it has yet to be demonstrated that the sense-organs of the left side are superior in persons left-handed. Nor has the inequality of the crossed pyramidal tracts in the adult been established with reference to these questions. Be this as it may, the lesions which cause aphasia or apraxia (inability to determine the meaning and use of objects) are predominantly in the left hemisphere in persons who are right-handed, while there is some evidence that the right hemisphere is more important in left-handed persons.

In the adult, damage to one hemisphere is usually followed by a permanent loss of function, but this loss may be transient when the lesion occurs in the very young subject, so that during the growing period the sound hemisphere can in a measure take up the function of the one that has been injured.

Assuming this general plan for the arrangement of the cortex to be correct, it is evident that a given cell, the neuron of which forms part of the pyramidal tract, must in the human cortex be subject to a large series of impulses coming to it over as many paths. Schematically, it would be as represented in Figure 198.

The discharging cell may be destroyed; then, of course, the muscles controlled by it become more or less paralyzed. The discharging cell may, however, remain intact, but the pathways by which impulses arrive at it be damaged. This is the type of lesion which produces symptoms of aphasia. When an interruption of associative pathways occurs some one or more of these tracts is broken, and hence this discharging cell does not receive a stimulus adequate to cause a response.

The physiological simplicity of the elements in any part of the central system, either when different portions of the system from the same animal or when the corresponding portions of different animals are compared, depends on the number of paths by which the impulses are brought to the discharging cells.

Composite Character of Incoming Impulses.—To these conclusions based on the anatomy are to be added others suggested by clinical observa-

[1] *Leitungsbahnen im Gehirn und Rückenmark*, 1876.

tions. That a patient suffering from a lesion between the visual and motor areas may be able to recognize an object and to indicate its use, it is sometimes necessary that the object shall appeal to several senses. For example, the name and use of a knife, when seen alone, may not be recalled, but when it is
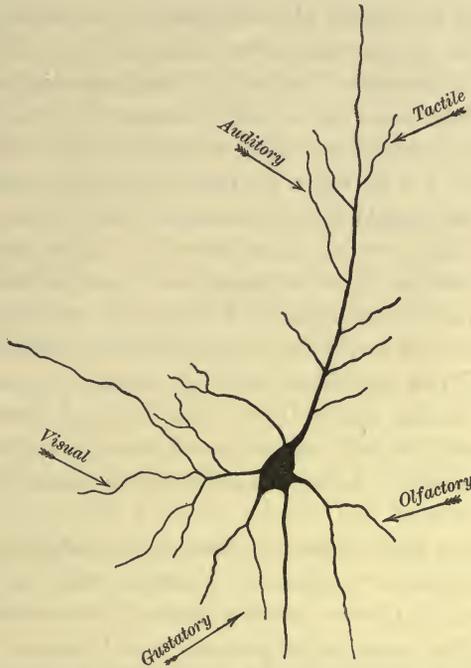
Fig. 198.—Schema showing in a purely formal manner the different sort of afferent impulses which may influence the discharge of a cortical cell.

taken into the hand—that is, when the dermal and muscular sensations are added to the visual one—the response is made, though, acting alone, any one set of sensations is inadequate to produce this result.

Just where the block occurs in such a case it is not possible to say with exactness, but the lesion lies, as a rule, between the sensory and motor areas concerned, and by the damage to the pathway, it is assumed that one or more groups of impulses are so reduced in intensity that they are alone insufficient to produce a reaction ; and therefore it is only when the impulses from several sides are combined that a response can be obtained.

Variations in Association.—It is a familiar fact that individuals differ in no small degree in the acuteness of their senses—*i. e.* in the power to discriminate small differences, and this, too, when the sense-organs are normal. Further, the powers of those best endowed are by no means to be attained by others, however conscientious their training. Moreover, the central sensory pathways differ widely. The inference is fair, therefore, that those who think in terms of visual images, as compared with those who think in auditory terms, do so by virtue of the fact that in the former case the central cells con-

cerned in vision are distinctly the better organized, while in the latter case it is those concerned in hearing.

In the same way, the power of expression varies in an equally marked degree, and the capacity for the expression of ideas by means of the hand in writing is by no means necessarily equal to the power of expression by means of spoken words. In the former case we have the results of the play of impulses from the several sensory centres on the motor area for the hand, and this is reinforced by the sight of that which has been written, whereas in the latter case impulses from these same sensory centres play upon the area which controls the muscles of phonation, and the reaction is reinforced by the sound of the words uttered. Of course in the case of a defective, like a blind-deaf-mute, the expression of thought is by movements of the fingers, and this is reinforced by the tactile and muscular sensations which follow these movements.

It is not by any means to be expected that the anatomical connections which render such reactions possible will be equally perfect for the different sensori-motor combinations or the same combinations in different persons, and hence the powers of the individual will be modified by the perfection of these paths in the several cases. From this it also follows that the same lesion as grossly determined will not produce identical results in the two persons, for it will not effect the damage of structural elements which are strictly comparable.

Pathways through Gray Matter.—Moreover, what is true of the spinal cord is also probably true of the cortex—viz. that while the long tracts are the usual and preferred pathways between centres, shorter tracts formed by a large series of cells often serve as the pathway, and impulses may under some conditions find their way from one part of the cortex to another by way of these more complex tracts.

Latent Areas.—It has been plain from an examination of the foregoing figures, as well as from the descriptions, that there must be a large portion of the cortex which, so far as has been observed, may be called latent. These regions, which include nearly the entire ventral surface of the hemispheres, a large part of the mesial surface, and on the dorsal and lateral aspects a large portion of the frontal and temporal lobes, certainly require a word.

The various forms of investigation yield negative results. The speech-centre is, strictly speaking, neither a motor nor a sensory portion of the cortex, and yet when it is damaged the function of speech is disturbed. We have come to look upon the speech-centre as containing cells by way of which impulses pass to the centres controlling the muscles of phonation. This relation suggests that the rest of the cortex called latent may act in a similar manner, and that by way of it pass impulses which modify the discharge of the motor areas proper. From any one portion of the latent area, however, the connections are not massive enough to permit of impulses which will cause a contraction, and hence these impulses coming from one locality to a discharging cell form only a fraction of the impulses which control it ; and for this reason the significance of these parts fails to be clearly evident upon direct experiment.

The cortex of the frontal lobes has some connections with the nuclei of the pons, and so with the cerebellum. The more recent experiments on the functions of this region are by Bianchi[1] and Grosglik,[2] the former on monkeys and dogs and the latter on dogs alone.

These experimenters found that the removal of one frontal lobe is comparatively insignificant in its effects, while when both are removed the change is profound. On removing the frontal lobe on one side only there is no disturbance of vision, hearing, intelligence, or character. There do occur both sensory and motor disturbances, but these are for the most part transient. On the side opposite to the lesion there is in the limbs a blunting of all sensations and some paresis. Moreover, there is a hyperæsthesia combined with a paresis of the muscles of the neck and trunk which move these parts *away* from the side of the lesion.

These several effects of the operation tend to pass off, and if then the remaining frontal lobe be removed from a dog or monkey, not only do the symptoms just described appear on the other side of the body, but still more fundamental changes occur. A ceaseless wandering to and fro, such as Goltz[3] observed in those dogs in which the anterior half of the brain had been removed, characterizes the animals; curiosity, affection, sexual feeling, pleasure, memory, and the capacity to learn are at the same time abolished, and the expressions of the animal are those of fear and excessive irritability. That, therefore, the frontal lobes play an important rôle in the total reactions of the central system is amply evident, but this by no means justifies the conclusion that they are the seat of the intelligence.

H. Comparative Physiology of the Central Nervous System.

For the better comprehension of the conditions found in man and the monkey, it will be of importance to briefly review the comparative physiology of the central nervous system in vertebrates below the monkey. This system in the lower vertebrates is usually composed of a very much smaller number of cells than is found in that of man, and also cephalization, or the massing of the elements toward the head and in connection with the principal sense-organs, has gone on to a far less extent.

It must not be thought, however, because it is the custom to emphasize the reflex activities of the lower vertebrates, and to show that these reflexes can be carried out even by fractions of the spinal cord alone, that therefore the spinal cord is particularly well developed in them. Comparative anatomy shows in the lower vertebrates a simplicity in the structure of the cord quite comparable with that found in the brain, and as we ascend the vertebrate series both parts of the central system increase in complexity. In this increase, however, the cephalic division takes the lead, and further, by means of the fibre-tracts, the cell-groups in the cord are more and more brought under the

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[1] *Archives Italiennes de Biologie,* 1895, t. xii.

[2] *Archiv für Anatomie und Physiologie,* 1895.

[3] *Ueber die Verrichtungen des Grosshirns,* 1881.

influence of the special sense-organs which connect with the encephalon. The physiological reactions of the higher vertebrates are especially modified by this latter arrangement. It is therefore true that the cord, as well as the brain, is, in man, more complicated anatomically than in any of the lower forms, and this in spite of the fact that the independent reactions of the human cord are so imperfect.

One result of this concentration of the nerve-elements toward the head, and the dependence of the rest of the system on the encephalon, is, as we shall see, that the cephalic division becomes thereby a more necessary portion of the pathway for the incoming impulses, and, conversely, as cephalization fails to take place the several parts of the system remain more independent.

Reactions of Portions of Spinal Cord.—When an amphioxus is cut into two pieces and then put back in the water, a slight dermal stimulus causes in both of them locomotory movements, such as are made by the entire animal.

When a shark (*Scyllium canicula*) is beheaded the torso swims in a co-ordinated manner when returned to the water. Separation of the cord from the brain does not deprive a ray (*Torpedo oculata*) of the power of perfect locomotion. The same is true of the ganoid fish. In the case of the cyclostome fish (*Petromyzon*) the beheaded trunk is, in the water, inactive, and, on gentle mechanical stimulation it makes inco-ordinated responses, but, put in a bath formed by a 3 per cent. solution of picro-sulphuric acid, locomotion under the influence of this strong and extensive dermal stimulus is completely performed. In the case of the eel the responsiveness even to the picro-sulphuric acid bath is evident in the caudal part of the body alone. In the bony fish this power in the spinal cord has not been observed.[1]

In these experiments the central system is represented by the entire spinal cord with the associated nerves, or by some fraction of it, but so simple, constant, and independent are the reactions of the cord under normal conditions that a strong stimulus is able to elicit the characteristic responses from even a fragment of the system. The higher we ascend in the vertebrate series the less evident do the independent powers of the cord become.

For the determination of the functions of the several parts of the nervous system it is possible to employ in animals the method of removal as well as the method of stimulation. The doctrine of localization was at one time crudely expressed by the statement that a cortical centre was one the stimulation of which produced a given reaction, and the removal of which abolished this same reaction. Goltz[2] soon showed that in the dog the removal of even an entire hemisphere did not cause a paralysis of the muscles on the opposite side of the body, although others had shown that a stimulation of certain portions of the cortex of the hemisphere would cause these muscles to contract. It was argued, therefore—and quite rightly—that the cortical centres of the dog did not completely answer to the definition.

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[1] Steiner: *Die Functionen des Centralnervensystems und ihre Phylogenese*, 2te Abth., "Die Fische," 1888.   [2] *Ueber die Verrichtungen des Grosshirns*, 1881.

From the experimental work of the strict localizationists like Hitzig,[1] Munk,[2] and Ferrier,[3] and from the work of those who, like Goltz[4] and Loeb,[5] denied a strict localization in the cerebral hemispheres, several important points of view have been developed.

In the first instance, anatomy indicates that in the central system there are but few localities which consist only of one set of cell-bodies, together with the fibres coming to these bodies and going from them. Almost every part has both more than one set of connections with other parts and also fibres passing through it or by way of it to other localities. Hence in removing any part of the hemispheres, for instance, not only are groups of cell-bodies taken away, but a number of extra pathways are interrupted at the same time, and thus the damage extends beyond the limits of the part removed. Moreover, when any portion of the central system has been removed there is a greater or less amount of disturbance of function following immediately after the operation ; but this disturbance partially passes away. There are thus " temporary " as contrasted with " permanent " effects of the lesion, and these require to be sharply distinguished, because it is the permanent loss which is alone significant in these experiments. Finally, it has been made clear that neither the relative nor the absolute value of any division of the central system is fixed, but depends on the degree to which cephalization has progressed, or, to use the more common measure, the grade of the animal in the zoological series, both expressions signifying an increase in the connections between the cerebrum
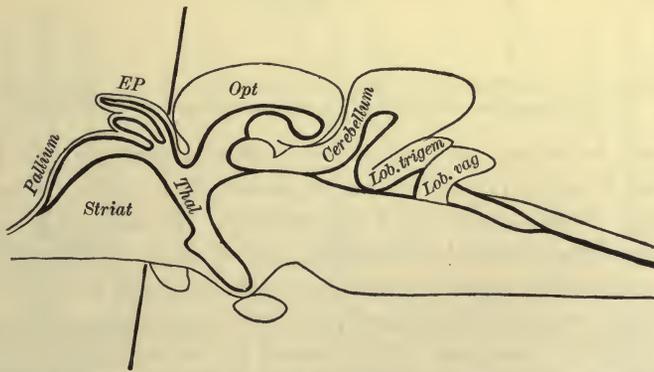
FIG. 199.—Schema of the encephalon of a bony fish—embryonic (Edinger). The vertical black line marks off the structures in front of the thalamus.

and the lower centres. The age of the animal on which the operation has been made is also of no small importance in this respect. These relations can be illustrated by reference to several experiments.

Removal of Cerebral Hemispheres.—If from a bony fish the cerebral

[1] *Untersuchungen über das Gehirn,* Berlin, 1874.
[2] *Ueber die Functionen der Grosshirnrinde,* Berlin, 1881.
[3] *The Functions of the Brain,* London, 1876.
[4] *Ueber die Verrichtungen des Grosshirns,* Bonn, 1881.
[5] *Arch. für die gesammte Physiologie,* Bde. 33 u. 34, 1884.

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hemispheres (including the corpora striata as well as the mantle) be removed, the animal apparently suffers little inconvenience.   The movements are undisturbed; such fish play together in the usual manner, discriminate between a worm and a bit of string, and among a series of colored wafers to which they rise, always select the red ones first.[1]   In these fish the eye is the controlling sense-organ, and, as will be recognized (see Fig. 199), the operation has by no means damaged the primary centres of vision.

Quite different is the result when the cerebrum is removed from a shark.[2] In this case, although the eyes are intact, the animal is reduced to complete quiescence; yet on the whole, the nervous system of the shark is rather less well organized and more simple than that of the bony fish.   The astonishing effect produced is explained by a second experiment (see Fig. 200).   If the
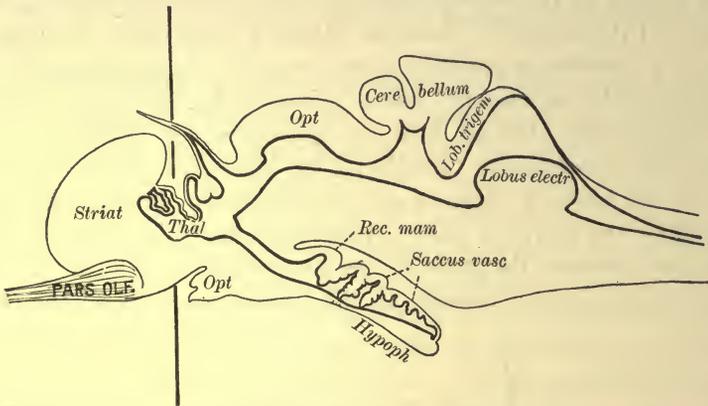
Fig. 200.—Schema of the encephalon of a cartilaginous fish (Edinger).   The vertical black line marks off the striatum and pars olfactorius, which lie in front of the thalamus.

olfactory tract be severed on one side, no marked disturbance in the reactions of the shark is to be noticed; when, however, both tracts are severed, the shark acts as though deprived of its cerebrum.   From this it appears that the removal of the principal sense-organ, that of smell, is the real key to the reactions, and that the responsiveness of the fish is reduced in the first instance, because in this case it has been deprived of the impulses coming through the principal organs of sense, and in the second the removal of the cerebrum is mainly important because the cerebrum contains the pathway for the impulses from the olfactory bulbs to the cell-groups which control the cord.

Passing next to the amphibia as represented by the frog, there are several series of observations on the physiological value of the divisions of the central system.   Schrader[3] finds the following: Removal of the cerebral hemispheres *only*, the optic thalami being uninjured, does not abolish the spontaneous activity of the frog.   It jumps on the land or swims in the water, and changes from one to the other without special stimulation.   It hibernates like a normal frog, retains its sexual instincts, and can feed by catching passing insects, such as flies

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[1] Steiner: *Die Functionen der Centralnervensystems*, 1888.   [2] Steiner, *loc cit.*
[3] *Archiv für die gesammte Physiologie*, 1887, Bd. xli.

(see Fig. 201). A frog without its hemispheres is therefore capable of doing several things apparently in a spontaneous way. Such frogs balance themselves
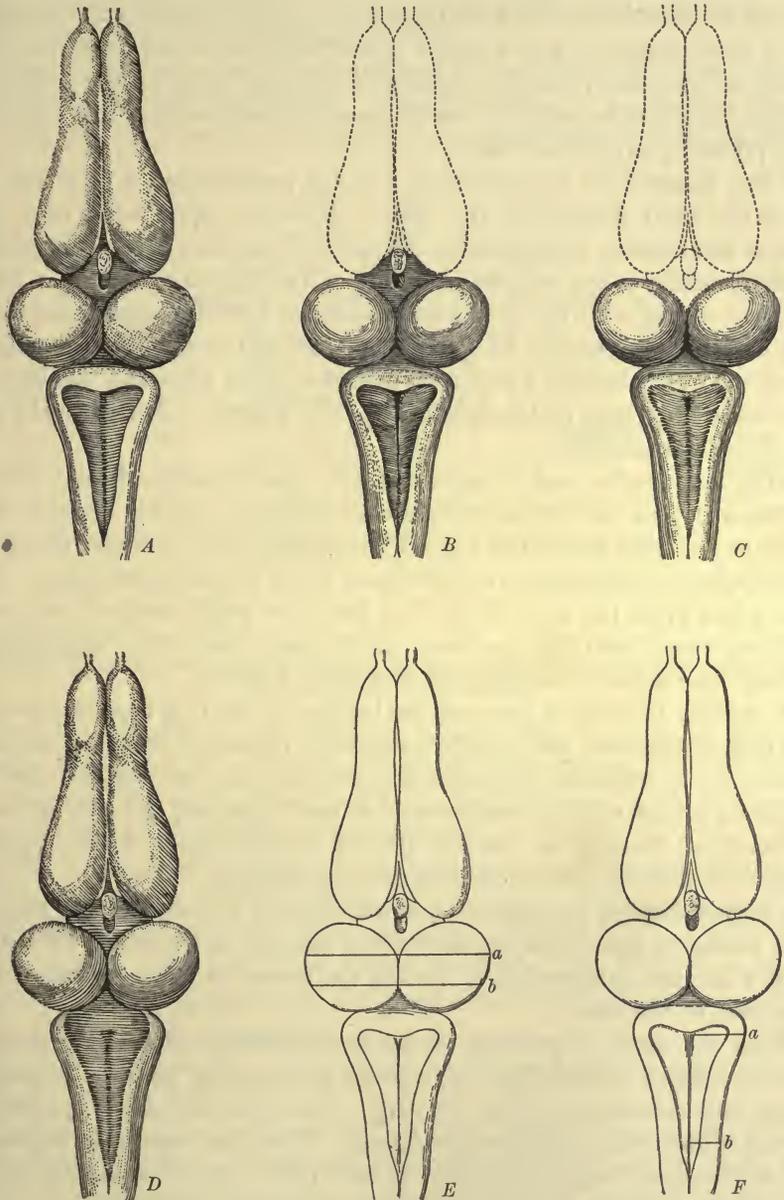
FIG. 201.—Frog's brain; the parts in dotted outline have been removed: *A*, brain intact; *B*, cerebral hemispheres removed; *C*, cerebral hemispheres and thalami removed; *D*, cerebellum removed; *E*, two sections through the optic lobes; *F*, two sections through the right half of the bulb (Steiner).

when the support on which they rest is slowly turned, moving forward or backward as the case demands in order to maintain their equilibrium. In doing

this the frog tends first to move the head in the direction opposite to the motion of the support, and then to follow with movements of the body. If the optic thalami are removed (Fig. 201, *C*), the power of balancing is lost, because, although the movements of the head still occur, those of the body are abolished. A frog thus operated on and deprived of the hemispheres and thalami exhibits the lack of spontaneity which is usually described as following the loss of the hemispheres alone, but which is not a necessary consequence of this operation, as the preceding experiments show.

A frog possessed of the mid-brain and the parts behind it (Fig. 201, *C*) will croak when stroked on the back. When the optic lobes have been removed this reaction becomes more difficult to obtain, but it is not necessarily abolished, neither is the characteristic fling of the legs in swimming. At the same time, a frog with its optic lobes can direct both its jumping and swimming movements according to light stimuli acting through the eye, jumping around and over obstacles which form a shadow in its path, and climbing out of the swimming tank on the lighter side. This power is lost when the optic lobes have been removed.

When the anterior end of the bulb (*pars commissuralis*—Stieda) has been also removed, then the frog becomes incessantly active, creeping about, and not coming to rest until he has run himself into some corner. Schrader found such frogs capable of clambering over the edge of a box 18 centimeters high. They are at a loss when the edge of the box has been finally attained, and vainly reach into space from this position. In the water they swim "dog-fashion," and only upon special stimulation do they make a spring.

If more of the bulb is removed, the bearing of the frog departs more and more from the normal, and is only temporarily regained in response to strong stimulation; nevertheless, co-ordinated movements can be obtained when the bulb down to the calamus scriptorius has been removed, and only when the movements of the arms are directly affected by the damage of the upper end of the cord does the inco-ordination become constant.

A section through the optic lobes at *a* (Fig. 201, *E*) puts the frog in a condition similar to that following the isolated removal of the lobes, while a section at *b* has the curious effect of causing the animal to move backward upon stimulation of the toes.

When the small ridge which forms the cerebellum in the frog has been removed, a slight tremor of the leg-muscles and a loss of precision in jumping are the only defects noted (Fig. 201, *D*). These results hold for symmetrical removal of the divisions of the encephalon. When the removal is unsymmetrical in the inter-brain, mid-brain, or bulb (Fig. 201, *F*, *a* and *b*), there is more or less tendency to forced positions or forced movements.

As a rule, action is most vigorous on the side of the body associated with the greater quantity of nerve-tissue. This relation appears as a natural result of the greater effectiveness of the incoming impulses when entering a larger group of central cells. Indeed, the removal of the different portions of the central system in the frog is accompanied by a progressive loss in responsive-

ness, stronger and stronger stimuli being required to induce a reaction. This holds true down to the anterior end of the bulb, the removal of which, on the contrary, sets free the lower centres, so that the frog becomes incessantly active. Just how this release is effected is not easy to explain, but further removal is again followed by the loss of responsiveness.

Passing next to the bird, as represented by the pigeon, the observations of Schrader are the most instructive.[1] The removal of the hemispheres from the bird (see Fig. 202) involves taking away the mantle and the basal ganglia, the
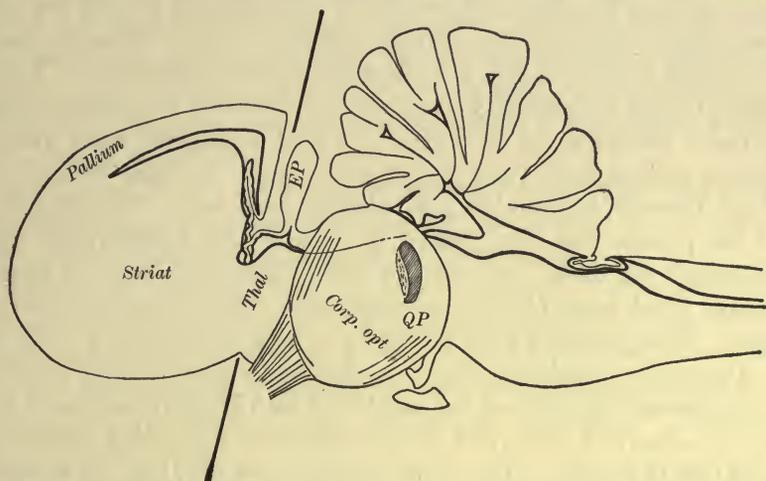
Fig. 202.—Schema of the encephalon of a bird (Edinger). The oblique black line marks off the structures in front of the thalamus.

chiasma and the optic nerves being left intact. For the first few days after operation the bird is in a sleep-like condition. Next the sleep becomes broken into shorter and shorter periods, and then the bird begins walking about the room. From the beginning its movements are directed by vision; slight obstacles it surmounts by flying up to them, larger ones it goes around. In climbing its movements are co-ordinated by the sense of touch, and the normal position of the body is maintained with vigor. The birds which walk about by day remain quiet and asleep during the night. In flying from a high place the operated pigeon selects the point where it will alight, and prefers a perch or similar object to the floor.

A reaction to sound is expressed by a start at a sudden noise, like the explosion of a percussion cap.

Pigeons without the cerebrum do not eat voluntarily, though the presence of the frontal portions of the hemispheres is sufficient to preserve the reaction.

In a young hawk slight damage to the frontal lobes abolished for the time the use of the feet in the handling of food, and thus abolished in this way the power of feeding as well as that of standing.

With the loss of the cerebrum the pigeon does not lose responsiveness to the objects of the outer world, but they all have an equal value. The bird is

[1] *Archiv für die gesammte Physiologie*, 1888, Bd. xliv.

neither attracted nor repelled, save in so far as the selection of the points toward which it will fly is an example of attraction. Sexual and maternal reactions both disappear, and neither fear nor desire is evident.

In ascending the mammalian series the removal of the cerebrum becomes a matter of increasing difficulty. The reasons for this are several, and reside in the increasing size of the blood-vessels and the nutritive complications dependent on the increase in the mass of the cerebrum, as well as in the greater physiological importance of this division. Goltz[1] has been able by repeated operations to remove the entire cerebrum of a dog, and still to keep the animal alive and under observation for eighteen months, at the end of which time the animal, though in good health, was killed for further examination. This dog was blind, though he blinked when a bull's-eye lantern was suddenly flashed in his face. He could be awakened by a loud sound, and when awake responded to such sounds when intense by shaking the head or ears. This would not, however, be complete proof that he could hear. The sense of taste was so far present that meat soaked in quinine was rejected after tasting. Tactile stimuli and those involving the muscle sense, as in the case when the animal was lifted, caused him to struggle and to bite in the direction of the irritation. These reactions were modified according to the locality of the stimulus. The power to make movements expressive of pain was still present.

On the motor side the dog was capable of such highly complicated acts as walking, standing, and eating, and in these operations was guided by the muscle sense and that of contact. The sexual instincts were lost, but the animal was excessively active, and became more and more excited when ready to defecate or when hungry.

The examination of the brain showed that all parts in front of the midbrain had been removed or were degenerated, so that the defects were due to a removal of rather more than the cerebrum proper.

Emotions, feelings, conscious sensations, or the capacity to learn were entirely wanting in this dog, and its reactions were those of a very elaborate machine.

If we compare, now, the effects of the removal of the cerebral hemisphere in the bony fish, the pigeon, and the dog, we see that the results of the operation are progressively more disturbing as we pass up the series. In the higher animals the effects are more often fatal, the disturbance immediately following is much more severe, the return of function slower, and the permanent loss greater. As a partial exception to the above statements is the observation that after operation the general health of pigeons always declines, and it is not possible to keep them alive more than about six weeks. On the contrary, a dog could be kept in good health for some eighteen months; but there is this difference, that the removal in the case of the dog was made by several successive operations.

By removal of the cerebrum the higher animal tends to lose just those capacities which best serve to distinguish it from the lower forms. When, therefore, the inquiry is made why the results gotten in the dog are not obtain-

[1] *Archiv für die gesammte Physiologie*, Bd. xli.

able in monkey or man, there are several replies. In the first place, no such extensive experiments have been made on monkeys of the right age and under equally favorable conditions. If a mature animal is taken, the secondary degenerations are so massive that they certainly cause great disturbance in the remaining part of the system. This is not equivalent to an assertion that the same results could be obtained in the monkey by more extensive experiments, but a suggestion of one difference behind the results thus far reported. There is no reason for assuming any deep-seated difference in the arrangement of the central system of the highest mammals as compared with that in the lower. Indeed, in some human microcephalic idiots the proportion of sound and functional tissue in the encephalon is less than one-fourth that found in a normal person, yet, on the other hand, no normal adult could lose anything like that amount of tissue which is out of function in these microcephalic brains and at the same time live.

The central system, therefore, even in man, is to be looked upon as possessed of some power to adapt itself when portions have been lost, but this is most evident when the defect begins early and develops slowly.

Keeping the cerebrum still in view, it is possible to go into further detail. In forms below the monkey the loss of portions of the cerebral cortex from the motor area is accompanied by a greater or less paralysis of the muscles represented. This, however, is an initial symptom only, and gradually disappears, though not always with the same completeness. In man, of course, the tendency to recover is least.

The anatomical relations behind this difference are the following: The efferent cells in the ventral horns are dominated principally by two sets of impulses, those arriving directly over the dorsal roots of that segment in which they are located, and those coming over the long paths by way of the cerebral cortex and pyramidal tracts. In the lower mammals this second pathway is insignificant, and when interrupted, therefore, the disturbance in the control of the ventral-horn cells is but slight. Passing up the series, however, this pathway tends to become more and more massive and important, as the figures previously given show (see p. 695), until in man and the monkey a damage of it such as is effected by injury to the cortex causes a high degree of paresis if not permanent paralysis, because by this injury a greater proportion of the impulses is thus cut off from the efferent cells.

It has previously been shown that the cortical areas do not vary according to the mass of the muscles which they control. Experiments also show that it is the fore limbs which are most disturbed in their reactions when the lesion involves the cortical centres for both fore and hind limbs, and this falls under the law that the more highly adaptable movements (*i. e.* those of the fore limb as contrasted with the hind limb) are most under the control of the cortex. If the examination be restricted to the fore limb alone, it is found that the finger and hand movements or those of the more distal segments are in turn the ones most disturbed. Thus, in the limbs, the more distal groups of muscles are those best controlled from the cortex. It follows, then, that for the

arm, paralysis of shoulder movements as the result of cortical lesion is least complete, while as we travel toward the extremity of the arm the liability to disturbance of its function as the result of cortical injury increases steadily.

Turning, now, to the "sensory" areas of the cortex, the principles underlying their physiological significance and connections appear to be similar. The lower the animal in the vertebrate series the more probable that its reactions can be controlled by the afferent impulses which have not passed through the cerebral cortex.

None of the senses except vision can be analyzed sufficiently to bring out the significance of subdivisions of the cortical area; hence the illustrations are taken from that sense alone.

It has already been shown that without cerebral hemispheres a bony fish can distinguish the colors of wafers thrown on the water and discriminate between a bit of string and a worm. In the same case a frog is able to direct its movements and to catch flies—*i. e.* to detect objects in motion and react to them normally. A pigeon can direct its movements in some measure, and even select a special object as a perch, but it is not able to respond to the sight of food or its fellows or those objects which might be supposed to excite the bird to flight. In the dog the vision which remains permits only the response of blinking when the eye is stimulated by the flash of a bull's-eye lantern. The progressive diminution in the response which follows visual stimuli in these animals is open to the interpretation that the path by which the impulses may pass over to the cells forming the primary centres intermediate between the sense-organ and the cortex is progressively diminished. Thus the impulses arriving at the primary optic centres are in a less and less degree reflected toward the cord, as the pathway to the cortex becomes more permeable. When therefore, the cortex has been removed the reactions taking place by way of it are disturbed in proportion to their normal importance.

In the first instance, when the reflexion occurs in the primary centres, the incoming impulses are distributed toward the cord by paths not known, while in the second, they pass from the cortex along the pyramidal tracts.

In the cortex subdivisions of the visual area have been made by Munk.[1] He found that the more anterior portions of the visual area were associated with the superior parts of the retina, and the more posterior portions with the inferior, while the area in one hemisphere corresponded with the nasal portion of the contralateral retina, and to a less degree with the temporal portion of the retina of the same side. The determination of these relations was made by the removal of parts of the visual area (dogs) and the subsequent examination of the field of vision. It appears, therefore, that the incoming impulses from certain parts of the retina are delivered at definite points in the cortex, and that when the paths are interrupted in the dog or higher mammals these impulses are blocked. By stimulation, it will be remembered, Schäfer determined similar relations in the monkey.

[1] *Ueber die Functionen der Grosshirnrinde,* Berlin, 1881.

Before leaving the cerebral hemispheres, mention of the fact should be made that still other functions, control of the sphincter ani (Fig. 189), secretion of saliva, and micturition can be roused by the stimulation of the cortex in the appropriate region—namely, in the region where the muscles and glands concerned might be expected to have representation if they followed the general law of arrangement. Changes in the production and elimination of heat from the body follow interference with the motor region of the cerebrum, and the removal of portions of the cortex in this region is followed by a rise in the temperature of the muscles affected.

In the encephalon, the cerebrum, and especially its outer surface, is the portion the functions of which have been studied. The significance of the other portions of the encephalon can be far less well determined. The disturbances caused by the section and stimulation of the callosum have been studied by Koranyi[1] and by Schäfer[2] and Mott. It was found that complete section of the corpus callosum was not followed by any perceptible loss of function. On the other hand, stimulation of the uninjured callosum from above gave symmetrical bilateral movements, while if the cortex on one side was removed stimulation of the callosum gave unilateral movements on the side controlled by the uninjured hemisphere. These results seem to corroborate the conclusion derived from histological work to the effect that the system of the callosum is composed only of commissural fibres and that it sends no fibres directly into the internal capsule of either side. Concerning the corpora striata and the optic thalami very little is known. In the case of the corpora striata injury causes in man no permanent defect of sensation or motion, although both forms of disturbance may at the outset be present in the case of acute lesions. Lesions of the corpora striata cause a rise in temperature.[3] Following a puncture of one corpus striatum there occurs in rabbits a rise amounting to some 3° C.: it begins a few minutes after the operation and may last a week, but the temperature tends to return to the normal. The most striking feature in these experiments is the very wide effects produced by an extremely small wound, like the puncture of a probe.

In the cases where lesion of the striatum on one side causes in man a rise of temperature it appears mainly on the side of the body opposite the lesion.[4] A vaso-motor dilatation occurs over the parts of the body where the temperature is high.

In less degree a rise of temperature follows injury of the optic thalamus— at least such is the result of experiments on rabbits—but the effect of the lesion is never so marked as in the case of the striatum. Owing to the disproportion between the area of the lesion and the extent of the effects, it is difficult to conceive of the anatomical relations which permit the reaction. It is of interest to note, however, that similar relations hold for the vaso-motor centre in the

[1] *Archiv für die gesammte Physiologie*, Bd. xlvii.   [2] *Brain*, 1890.

[3] Aronsohn und Sachs: *Archiv für die gesammte Physiologie*, 1885, Bd. xxxvii.; Richet: *Compt. rend. de l'Acad. des Sciences*, 1884; Ott: *Brain*, 1889, vol. xi.

[4] Kaiser: *Neurologische Centralblatt*, No. 10, 1895.

bulb, in which case the vessels supplying a great area are controlled by a small group of cells.

The difficulty of an anatomical explanation is increased by the fact [1] that Ott enumerates in animals six heat-centres : 1. The cruciate, about the Rolandic fissure ; 2. The Sylvian, at the junction of the supra- and post-Sylvian fissures ; 3. The caudate nucleus ; 4. The tissues about the striatum ; 5. A point between the striatum and the thalamus, near the median line ; 6. The anterior mesial end of the thalamus.

The only other division of the encephalon, the functions of which can properly be described apart, is the cerebellum.   This portion is among vertebrates almost as variable in its development as the mantle of the cerebral hemispheres, and in many fish and mammals is asymmetrical in its gross structure.

The recent work on this subdivision has been carried out in the first instance by Luciani,[2] and later by Russell [3] and by Ferrier.[4]

The cerebellum is not concerned with psychical functions.   The removal of it does not cause permanently either paralysis or anæsthesia, but the immediate effects of an extensive injury are a paresis and analgesia as well as anæsthesia mainly in the hind legs, and in consequence a high degree of incoördination in locomotion.   A distinct series of symptoms, however, follows injury to this organ, and these are modified according to the locality and nature of the lesion.   Removal of one half (cerebellar hemisphere plus half the vermis) of the cerebellum in the dog causes a deviation outward and downward of the optic bulb on the opposite side, a proptosis of the bulbs on both sides, nystagmus and contracture of the muscles of the neck on the side of the lesion, and an increase of the tendon reflexes in the limbs.   In walking the dog wheels toward the side opposite to the lesion, and tends to fall *toward* the side of the lesion.

The symptoms are chiefly unilateral, and, caudad from the cerebellum, are on the side of the lesion.   The symptoms are less severe when only one hemisphere, instead of an entire half of the cerebellum, has been removed.   The existing symptoms are not intensified by the removal of the remaining half. The permanent condition of the muscles after operation is expressed by an atonia, or lack of tonus, in the resting muscles ; an asthenia, or loss of strength, which was measured by Luciani, and was most marked in the hind leg ; an astasia, or a lack of steadiness in the muscles during action ; and finally an ataxia, or a want of orderly sequence, in the contractions of a muscle-group.   The general expression of these symptoms is a twist of the trunk, the concavity being toward the operated side, combined with a disorderly gait. At the same time there is no demonstrable permanent disturbance of tactile or muscular sensibility.

Though the two halves of the cerebellum are united by strong commissural fibres, the complete division of the organ in the middle line is followed by a disturbance of the gait which is only transitory.   Hence it is inferred that the

[1] Ott : *loc. cit.*   [2] *Archives Italiennes de Biologie,* 1891–92, xvi.
[3] *Philosophical Transactions Royal Society,* 1894.   [4] *Brain,* 1893, vol. xvi.

connections of the cerebellum are mainly with the same side of the bulb and spinal cord. Cephalad of the cerebellum the connection, however, is a crossed one, each cerebellar hemisphere being associated with the contralateral cerebral hemisphere. Throughout these connections, both cephalad and caudad to the cerebellum itself, it appears that there is always a double pathway, and the cerebellum not only sends impulses to, but receives them from, the regions with which it is associated.

One effect of removal of one half of the cerebellum is to increase the responsiveness of the cortex of the contralateral cerebral hemisphere to electrical stimulation, thereby making it possible with a weaker stimulus to obtain a reaction which could be obtained from the other hemisphere only by a stronger one. When an irritative lesion is made, instead of a merely destructive one, the rotation and falling are away from the side of the lesion instead of toward it.

The experiments altogether show the cerebellum to be closely associated with the proper contraction of the muscles, and this is so directly connected with the maintenance of equilibrium that it is not surprising to find that stimulation or removal of the cerebellar cortex, besides producing nystagmus, may give rise to deviations of the eyes similar to those found on injury to the semicircular canals or stimulation of their nerves in fishes.[1]

PART III.—PHYSIOLOGY OF THE NERVOUS SYSTEM TAKEN AS A WHOLE.

A. WEIGHT OF THE BRAIN AND SPINAL CORD.

In attributing a value to the mass of the nervous system we assume that the elements which compose it possess potential energy. This energy varies for any given element in accordance with a number of conditions, but for the moment it will be sufficient to point out that if the mass of the entire system is significant the masses of its respective subdivisions are also significant, as showing in some measure the relative physiological importance of the several parts.

Changes Dependent upon Age.—That the mass of the system varies with age is a matter of common observation. The changes which occur in the mass, although they are specially evident, are not the only changes which take place; for with the change in mass go hand in hand changes in the relations which the elements bear to one another, and which result in making the organization of the system different at the different periods of life. Moreover, the specialization of the nerve-elements, in the mammals at least, has been carried to such a point that they are utterly dependent for their full activity on the nutritive system, and the character and amount of the nutrient plasma is a circumstance of prime importance. Any variation in this factor serves to completely alter the activities of the system, be it never so well organized, and

[1] Lee: *Journal of Physiology*, 1893, vol. xv.; 1894, vol. xvii.

therefore the discussion of the general powers of the nervous system for performance must never leave this factor unconsidered.

Constituents of the Central System.—Calculation shows that the cell-bodies probably contribute less than 10 per cent. of the entire weight of the central system, so that the remainder must be made up of neurons and other tissues.

In the central system there are present, besides the nerve-elements proper, the sustentacular tissues and the nutritive vessels—the channels for blood and lymph. Just what fraction of the total weight of the central system is thus represented has not been exactly determined, but it must be nearly equal to that of the nerve cell-bodies alone.

The weight of the brain is the weight of these several constituents.

Of course a brain congested with blood would weigh more than one from which the blood had been largely withdrawn, but there is no way of controlling this condition directly. Previous to weighing, the brain is sometimes subdivided and even cut into large sections, in which case of course much of the blood and lymph has the opportunity to drain away. In some cases too the brain is weighed without, and in others with, the pia.

Weight of the Pia and Fluid.—Broca's table for the weight of the pia in males is as follows:[1]

20–30 years	. . . . 45 grams.
31–40 "	. . . . 50 "
60 "	. . . . 60 "

The cast of the ventricles, as made by Welcker, displaces 26 cubic centimeters of water, so that the fluid filling these cavities would weigh a trifle over 26 grams.

Percentage of Water.—In man the percentage of water in the gray matter of the cerebrum is 81.8 per cent., and in the white matter 70 per cent.[2]

Specific Gravity.—According to calculation, the specific gravity of the entire encephalon is 1036.3 in the male and 1036.0 in the female. Obersteiner[3] found the specific gravity of the cortex to gradually increase from frontal to the occipital lobe. It was further found that while the outermost layer of the cortex had a specific gravity of 1028, that of the middle layers was 1034 and of the deepest layers 1036, thus indicating a progressive increase from the most superficial to the deepest layers—an increase to be associated with the larger proportion of medullated fibres in the deeper layers.

Weight of the Encephalon and Spinal Cord.—As a result of the preceding statement it follows that when the weight of any portion of the nervous system is taken, the final record represents, in addition to the weight of the nerve-tissues proper, that of the supporting and nutritive tissues, together with the enclosed blood and lymph. It is, however, assumed that under normal conditions the relation between the nervous and non-nervous tissues is

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[1] Broca, quoted by Topinard: *Eléments d' Anthropologie générale,* 1885.
[2] Halliburton: *Journal of Physiloogy,* 1894.   [3] *Centralblatt für Nervenheilkunde,* 1894.

nearly a constant one, and that the results of different weighings are therefore comparable among themselves.

Interpretations of Weight.—Assuming as the simplest case that the number of the nerve-elements composing a given portion of the central system is constant, then differences in the weight of these portions in different individuals imply variations in the size of the component cells. The significance of variations in the size of the nerve-elements must be, primarily, that the larger the cells, and especially the larger the cell-bodies, the greater the mass of cell-substance ready at any moment to undergo chemical change leading to the release of energy. On the other hand, if the number of elements is variable, an increase in the number must, in view of the law of isolated conduction, also provide a larger number of conducting pathways. Whether this increase in the number of pathways shall further add to the complication of the system depends on the localities at which it occurs. Bearing these facts in mind, we may turn to the records of the weight of the encephalon.

Weight of the Encephalon.—The encephalon is that portion of the central nervous system contained within the skull. The accompanying diagram
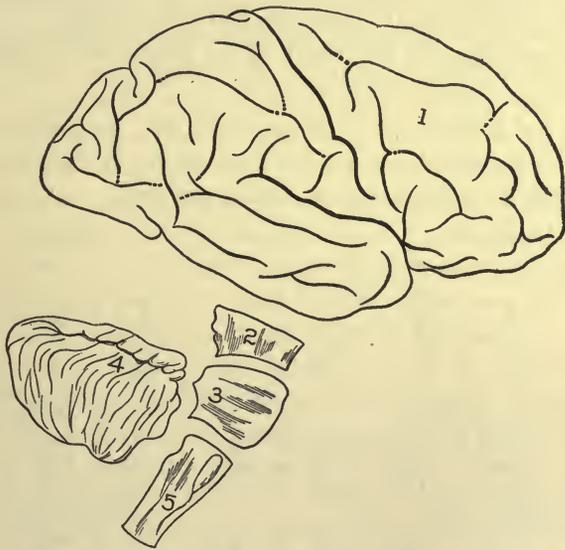
FIG. 203.—Showing the principal divisions of the encephalon made for the study of its weight: 1, hemisphere seen from the side, fissuration according to Eberstaller; 2, mid-brain, region of the quadrigemina; 3, pons; 4, cerebellum, or hind-brain; 5, bulb, or after-brain. Divisions 2, 3, and 5, taken together, form what is designated the "stem" in the tables of Boyd (modified from *Quain's Anatomy*).

(Fig. 203) shows the encephalon, together with one manner of subdividing it. Its weight has usually been taken while it was still covered by the pia, but after allowing the fluids to drain away for five minutes or more. As has been stated, sometimes drainage has been facilitated by cutting into the brain; hence, when the brain-weight records by any observer are to be discussed, the first question concerns the method according to which the brains were examined, for the weights may be either with or without the pia and with or without drainage.

The anthropologists classify the encephala according to weight in the following manner:

The Nomenclature of the Encephalon according to Weight.   Weight in Grams (Topinard).

Classes.	Males.	Females.
Macrocephalic	From 1925–1701	From 1743–1501
Large	" 1700–1451	" 1500–1351
Medium	" 1450–1251	" 1350–1151
Small	" 1250–1001	" 1150– 901
Microcephalic	" 1000– 300	" 900– 283

The brain-weight in the majority of persons falls within the group of medium brains, and average figures are obtained by combining the individual records in which all variations from the medium occur. Of course races of small size, like the small people of India or the Pygmies of Africa, would not be expected to possess encephala equal in weights to those of the larger races of Europe. Any set of average figures, therefore, should be based as nearly as possible on observations made on a homogeneous population. Within the limits of a given race there are several conditions which determine differences in brain-weight, namely, sex, age, stature, and body-weight.

From the observations by Dr. Boyd on the weight of the brain in England the following table has been compiled:

Table showing the Weight of the Encephalon and its Subdivisions in Sane Persons, the Records being arranged according to Sex, Age, and Stature (from Marshall's tables based on Boyd's records).[1]

		MALES.					FEMALES.			
Ages.	Encephalon.	Cerebrum.	Cerebellum.	Stem.	Stem.	Cerebellum.	Cerebrum.	Encephalon.	Ages.
Stature 175 cm. and upward.					Stature 163 cm. and upward.				
20–40	1409	1232	149	28	23	134	1108	1265	20–40
41–70	1363	1192	144	27	23	131	1055	1209	41–70
71–90	1330	1167	137	26	24 *a*	130	1012	1166	71–90
Stature 172–167 cm.					Stature 160–155 cm.				
20–40	1360	1188	144	28	26 *s*	137 *s*	1055	1218	20–40
41–70	1335	1164	144	27	26 *s*	131	1055	1212 *s*	41–70
71–90	1305	1135	142 *s*	28 *a s*	24	128	969 *s*	1121	71–90
Stature 164 cm. and under.					Stature 152 cm. and under.				
20–40	1331	1168	138	25	24 *s*	130	1045	1199	20–40
41–70	1297	1123	139 *a*	25	25 *a s*	129	1051 *a*	1205 *a*	41–70
71–90	1251	1095	131	25	25 *a s*	123	974	1122	71–90

The method of weighing the brain used by Dr. Boyd[2] was as follows: The skull-cap being removed and the pia being intact, the hemispheres were sliced

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[1] *a* indicates that a record considered according to age is too large; *s* indicates that a record considered according to stature is too large.

[2] *Philosophical Transactions of the Royal Society*, London, 1860; see also Marshall: *Journal of Anatomy and Physiology*, 1892.

away by horizontal sections as far down as the tentorium. The parts of the hemispheres still remaining were then removed by a section passing in front of the quadrigemina. The cerebellum was next separated from the stem, this latter being represented by the quadrigemina, the pons, and the bulb. Each hemisphere, the cerebellum, and the stem were then weighed separately.

Between the twentieth year and old age there are here represented the average encephalic weights, arranged in two main groups according to sex, and then in large horizontal groups according to stature, those of a given stature being subdivided according to age. This record is typical of what has been found by other observers and may be discussed without further evidence.

If groups of similar ages and corresponding statures are compared according to sex, it is at once seen that the male possesses the heavier encephalon, and that all the subdivisions of it are likewise heavier.

When individuals of the same sex and falling within the same age-limits are compared according to stature, those having the greater stature are found to have the greater brain-weight, though in the case of the subdivisions of the encephalon, and especially among the females, there are some irregularities, but these would probably disappear could the number of observations be increased. Finally, within the groups of those having the same stature, but different ages, the weight decreases with advancing age. The middle group, forty-one to seventy years of age, is in one way unfortunate, because, while the brain is probably still growing (see curve of growth, Fig. 204), during the first third of that period, and is nearly stationary (males especially) during the second, it begins to diminish so rapidly during the last third that the average weight is lower for the cases between sixty-one and seventy years than for the twenty years between forty-one and sixty years. Between seventy-one and ninety years the involutionary changes in the central system are most marked, and the decrease in weight during this period is clearly indicated.

Body-weight.—As regards the relations between the weight of the central system and the weight of the body the case is not so clear. In the first place, the presence of fat at maturity disturbs the results, because the nervous system cannot be expected to vary with changes in the quantity of an inactive tissue representing stored food-stuff merely. The taller individuals have a larger cranial capacity than the shorter, and hence the variation of brain with body-mass can only be made fairly when persons of the same stature, but of different body-weights, shall have been carefully compared.

If under these circumstances it shall appear that the bulkier individuals have the heavier nervous system, then the excess in their favor can be fairly correlated with the excess of the active tissues.

Before suggesting an explanation of these variations according to age, sex, and stature, it is to be noted that they occur in other mammals as well as in man. As regards the difference in the weight of the encephalon due to sex, it has been shown to obtain among the apes,[1] the male having the heavier brain; and from the general relation of size according to sex among the mammalia,

[1] Keith: *Journal of Anatomy and Physiology*, 1895.

where the male as a rule has the greater body-weight, it is to be anticipated that a similar difference in the weight of the brain will be shown in other groups.

Among individuals of the same species, but of different races or of different lengths and weights, the law holds good that the larger races have the heavier brains, as do the larger and heavier individuals. Here, as in the case of man, it is always assumed that the differences in body-weight are mainly correlated with the active tissues like muscle, and not with fat. As to the loss of the brain in weight after maturity, observations on animals are scanty, but point to decrease in weight toward the natural close of life.

Interpretation of Brain-weight.—In the absence of fuller data the explanation of the series of differences just mentioned is, in a very high degree, tentative. The loss of weight in advanced years appears to be due to a general atrophy of the nerve-elements. The greater brain-weight associated with greater stature appears to depend on the variations in the size of the elements rather than in their number, and, so far as can be seen, the distinction according to sex is susceptible of a similar explanation.

The fact that the difference in brain-weight between the two sexes more probably depends upon a difference in the size of individual elements than upon a difference in the number of these elements is strongly suggested by the following considerations: The microcephalic brains, constituting one group which always appears in long series of records, belong to individuals whose intelligence is very limited or to those to whom the functions necessary to mere existence are just possible. In this latter class we have presumptively arrived at a brain in which the functional elements are reduced to the lowest number compatible with life.

Subjoined is a table giving the average weights of microcephalic brains for the two sexes, the observations being divided into three groups. In each of the groups taken the average weight for the females is less than that for the males:

The Weight of the Brain in Microcephalics (condensed from Marchand).[1]

Group.	241–500 grams.	501–800 grams.	801–1015 grams.
Males	349	651	954
Females	299	621	912

When the weight for the two sexes is here compared, it is seen that the average for the female is the closer to the lower limit in each group. As by hypothesis we are dealing with the least possible number of elements in either sex, and as there is no reason to assume that this minimum number is materially different for the two sexes, the inference is plausible that in these cases the difference in weight is in a large measure due to the difference in the *size* of the constituent elements. If this holds for the lower limit of the series, it is of course also probable that it holds throughout the entire series as well.

As compared with the average brain, those of either sex forming the groups heavier than the average owe their greater weight more often to an increase in the size of the constituent elements than to an increase in their number. On

[1] Marchand: *Nova Acta der Kaiserl. Carol. Deutsch. Akad. der Naturforscher*, Halle, 1890.

the other hand, in those groups possessing the smallest weight not only the size, but more probably also the number, of elements may be reduced below that found in normal persons. These statements are of course to be applied for the present to members of the same race. We know that the mammals with smaller nervous systems than that of man have a far smaller number of nerve-cells composing them.

It is probable that the wider variations in the number of cells composing the nervous system in man occur among the different races, and that here, as well as among the microcephalics, in which development has been early arrested, differences in the number of cells are most marked.

Weights of Different Portions.—A study of the proportional weights of the several subdivisions of the encephalon according to the sex, stature, and age shows that there is very little difference caused by variations in these conditions. This too, so far as it goes, suggests that the absolute weight is dependent rather on variations in the size than in the number of the elements, since a harmonious variation in number would be less probable than a harmonious variation in size.

Social Environment.—It is not to be expected that the weight of the brain among the least-favored classes in any community will be the same as that of those who, during the years of growth, are under favorable conditions. All extensive series of observations which we possess relate to the least-favored social classes, and hence it is not improbable that the figures in the foregoing tables, which are based on data obtained mainly at the Marylebone workhouse in London are decidedly below those which would be obtained from the more fortunate classes in the same community. We have a list of brain-weights which contains the records for a number of men of acknowledged eminence, and also for others who attained recognition as able persons without being exceptionally remarkable. It shows the men in this list to have brains on the average heavier than the usual hospital subject.[1]

Comparison of the brain-weights of eminent men with the weights taken from the classes used to furnish the standard has been made by Manouvrier. The table on page 722 gives the brain-weights occurring among eminent men compared with those found among Parisians of the lower classes, these latter being subdivided according to stature (Manouvrier). The figures express the number of brains in each group of 100 that would fall within the limits of weight opposite to which the entries stand.

There is a wide range in the weights given in these tables, but at the same time their average is high as compared with the figures of Boyd and other observers. Since even those who are undoubtedly distinguished present brain-weights having a wide range, and since any long series of observations would furnish a fair number of cases of high brain-weight without any suggestion of superior mental ability, it is evident that the high brain-weight and unusual mental capability are by no means necessarily linked—a conclusion in harmony with common observation. Whether, however, high brain-

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[1] Donaldson : *The Growth of the Brain,* 1895.

weight is to be considered more frequent among men of distinction cannot be determined until there is available a large number of records obtained, not from the less-favored social classes, but from persons accounted as successful merchants, bankers, and members of the learned professions.

Weight of the Encephalon. in Grams.	Parisians of Broca. Adult. 168 cm.	Parisians of Tall Stature. 171–185 cm.	Eminent Men.		
			1st Series.	2d Series.	Series 1 and 2 combined.
900–1000	0.6				
1001–1100	0.6				
1101–1200	7.1	3.5	. .	2.9	1.2
1201–1300	23.3	15.5	11.1	2.9	7.5
1301–1400	31.5	27.5	17.8	17.2	17.5
1401–1500	23.8	34.6	33.3	48.5	40.0
1501–1600	9.6	15.5	24.5	22.8	23.8
1601–1700	3.5	3.4	2.2	5.7	3.3
1701–1800	. .	. .	2.2	. .	1.6
1801–1900	. .	. .	2.2	. .	1.3
1901–2000					
2001 and more	. .	. .	6.7	. .	3.8
Total	100	100	100	100	100

Brain-weight of Criminals.—The observations of Manouvrier have shown that among French murderers the brain-weight is similar to that of the individuals usually examined in the Parisian hospitals. In the same manner, the observations on the brain-weight among the insane indicate, according to the records of Boyd and others, that the insane as a class (the microcephalics being of course excluded) are not characterized by a special brain-weight. When, however, the insane are grouped according to the special diseases from which they have suffered, it is evident that those in which the brain was congested at death exhibit the higher weight, while those in which the pathological processes caused destructive changes exhibit a low weight. The differences in these cases are rather the results of disease than the cause of it.

Brain-weights of Different Races.—Concerning the weights of the brain in different races there are no extensive observations which have been made directly on the brain itself. Davis[1] has, however, determined the cranial capacities of a series of skulls belonging to different races, and the brain-weights as calculated from these are as follows:

Races.	MALES.				FEMALES.			
	No. of Cases.	Heaviest.	Lightest.	Average.	Average.	Lightest.	Heaviest.	No. of Cases.
European	299	1364—1212		1340	1180	1099—1278		94
Oceanic	210	1369—1192		1293	1185	1139—1239		95
American	52	1338—1209		1282	1164	1087—1263		31
Asiatic	124	1397—1155		1278	1171	1042—1276		86
African	53	1316—1165		1268	1187	1100—1220		60
Australian	24	1414—1027		1190	1089	966—1194		11

[1] *Journal of the Academy of Natural Science*, Philadelphia, 1869.

This, as will be seen, gives the largest brain-weights to the western Europeans, but for a proper interpretation of the results there are needed at least the data concerning stature and age of the cases studied, both of which are here lacking.

Weight of Spinal Cord.—Comparatively few observations are available for the spinal cord: Mies[1] found that in adults it weighed 24 to 33.3 grams, with an average weight of 26.27 grams: this for the cord deprived of the nerve-roots, but covered by the pia. The variations due to sex and stature have not been determined. It seems probable, however, that the cord, like the brain, will be found lighter in females and in short persons: Mies states that its decrease in old age is proportionately less than that of the brain.

Bilateral Symmetry as determined by the Balances.—The central nervous system in its larger features is bilaterally symmetrical. In detail, however, there are many deviations. The question at once arises whether these variations are normally wide enough to permit us to attach to them a distinct physiological value. While, morphologically, bilateral symmetry is expressed in the arrangement of the central system, common experience and clinical observations show that most persons are physiologically one-sided, and the two sets of facts are apparently out of harmony, provided an anatomical basis is sought for the physiological reactions. The facts bearing on this question are the following:

The two cerebral hemispheres in man are found to weigh within a gram of one another in about one-third of the cases recorded (Franceschi). Larger differences, when found, are not distinctly in favor of either hemisphere, according to the observations of this same author. The results of those observers who have found one side constantly heavier are discordant.

In individual cases, of course, wide differences between the weight of the two hemispheres may occur, but these are clearly abnormal.

Asymmetry Otherwise Determined.—Other asymmetry has not been detected by the balances. The human cerebellum has not been studied in reference to its bilateral symmetry, but in cats Krohn[2] found the molecular layer thinner on the right side, and the same is true in the case of the sheep. In both these animals the middle lobe (vermis) is, however, asymmetrical, being twisted to the right, and it is just possible that the thickness of the molecular layer may be associated with this arrangement. Flechsig's observations on the asymmetry of the pyramidal tracts have already been noted.

In connection with these anatomical results it is to be noted that the blood-supply to the anterior portions of the left hemisphere is through the left carotid, which appears mechanically fitted to furnish a more direct supply than does the right; and, bearing in mind the dominant influence of nutritive conditions for nervous response, this arrangement may yet prove to be significant.

The few data which are available on the asymmetry of the central system do not therefore give us a basis sufficient to explain the asymmetry of function.

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[1] *Neurologische Centralblatt*, 1893.
[2] Krohn: *Journal of Nervous and Mental Disease*, 1892.

B. Growth-changes.

The characters of the brain and cord thus far described have been those found for the most part in the adult. Between birth and the natural end of life, however, great changes take place, and, as it is necessary to consider the functions of the central system at all times in its history, the importance of knowing the direction in which the growth-changes are probably occurring is obvious.

Growth of Brain.—The weight of the brain from birth to the twenty-fifth year is given below (Vierordt[1]).

Increase in Brain-weight with Age—Encephalon Weighed Entire with Pia (compiled by H. Vierordt).

Age.	Males.		Females.	
	No. of Cases.	Brain.	Brain.	No. of Cases.
0 months	36	381	384	38
1 year	17	945	872	11
2 years	27	1025	961	28
3 "	19	1108	1040	23
4 "	19	1330	1139	13
5 "	16	1263	1221	19
6 "	10	1359	1265	10
7 "	14	1348	1296	8
8 "	4	1377	1150	9
9 "	3	1425	1243	1
10 "	8	1408	1284	4
11 "	7	1360	1238	1
12 "	5	1416	1245	2
13 "	8	**1487**	1256	3
14 "	12	1289	**1345**	5
15 "	3	**1490**	1238	8
16 "	7	1435	1273	15
17 "	15	1409	1237	18
18 "	18	1421	1325	21
19 "	21	1397	1234	15
20 "	14	1445	1228	33
21 "	29	1412	1320	31
22 "	26	1348	1283	16
23 "	22	1397	1278	26
24 "	30	1424	1249	33
25 "	25	1431	1224	33
Total number of cases, 415.			Total number of cases, 424.	

From the same figures the first part of the accompanying curve (Fig. 204) has been formed.

The curve beyond the twenty-fifth year is continued on the basis of the observations by Bischoff,[2] and for comparison the curve representing the encephalic weights of a series of eminent men, forty-five in number, is drawn in a dotted line, the averages for decennial periods being alone plotted.

These records exhibit the fact that at birth the weight of the brain is about one-third of that which it will attain at maturity. The increase is very rapid during the first year, and vigorous for the first seven or eight years, after which it becomes comparatively slow. The maximum weight is indicated in the

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[1] *Archiv für Anatomie und Physiologie*, 1890.   [2] *Hirngewicht des Menschen*, Bonn, 1880.
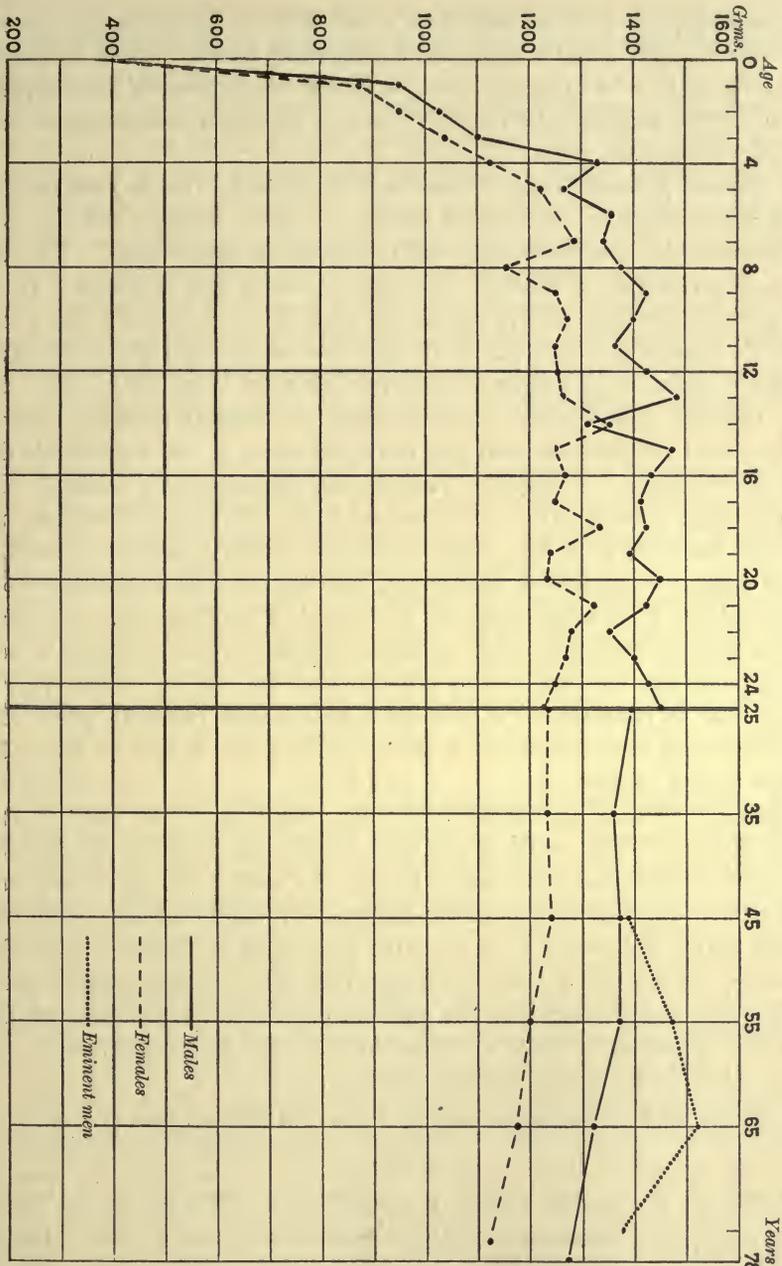
Fig. 204.—Curves for each sex, showing the weight of the brain according to age. For the first twenty-five years the curve is formed from annual averages based on the figures of H. Vierordt; from twenty-five years on the curves are formed from decennial averages based on the observations of Bischoff. All the data are from observations on the less fortunate classes. The dotted curve for eminent men is formed from decennial averages based on forty-five observations.

fifth decade (males), fourth (females), although there is a premaximum in the middle of the second decade (at thirteen and fifteen years for males and fourteen years for females), in which the too early and too vigorous growth of the

encephalon appears to be an important factor in the cause of death; hence the larger brain-weight found at autopsies during these years. While, in general, the individual may be supposed to follow in the development of his encephalon the course here indicated by the curve, this premaximal increase must be excepted for the reasons given.

It appears probable, from various lines of research,[1] that individuals differ widely in the length of time during which the brain enlarges, and also in the time at which the atrophic changes due to old age become evident. The curve for the brain-weight of eminent men also points in this direction. In this latter group the atrophy of old age does not become evident until the sixtieth year. To explain this, it must be remembered, as has been previously stated, that the records of the weight of the brain, such as those here quoted from Boyd, Bischoff, and Vierordt, are all based on hospital autopsies made in densely-settled communities, and that the social status of the individuals there examined was that of a class least vigorous and least favorably situated. It is not surprising, therefore, that when compared with the group of eminent men, both vigorous and, as a rule, more favorably situated, not only should the average weight be greater in this group, but, what is more important, growth should continue for a longer time and the period of senile atrophy be deferred.

If, as appears probable, these differences depend on the favorable or unfavorable conditions existing during growth, then it will be evident that the average man is possessed of a nervous system which probably grows for a longer time and resists decay to a later age than the figures of Bischoff or of Boyd would suggest.

Weight of Brain at Birth.—The older records gave the male child the heavier brain at birth, while the newer records, like those of Vierordt and others, give the reverse. Be this as it may, the weight at birth is seen to be nearly alike in the two sexes, and the difference in weight becomes distinct and increases during the period of most active growth up to maturity, from which time to the end of life this difference between the sexes remains nearly constant.

The proportional weights of the different parts according to the method of subdivision practised by Boyd are here shown. The figures indicate the percentage values of the parts of the encephalon:

Weight of the Encephalon and its Parts at Different Ages (Boyd).

No. of Cases.	Age.	Cerebrum.	Cerebellum.	Stem.
	MALES.			
45	New-born.	92.4	5.8	1.60
22	7 to 14 years.	87.8	10.3	1.61
99	30 " 40 "	87.3	10.6	1.98
95	70 " 80 "	87.0	10.7	2.09
	FEMALES.			
45	New-born.	92.1	6.2	1.50
18	7 to 14 years.	87.9	10.5	1.50
80	30 " 40 "	87.0	10.8	2.01
128	70 " 80 "	86.9	10.9	2.15

[1] Galton: *Hereditary Genius*, 1884; Venn: *Nature*, 1890.

The table indicates a proportional relation at birth, and probably for a short time after, different from that found at maturity, but this very early approximates that found in the adult.

Relation between Growth of Body and Encephalon.—When the curve of growth for the entire body is compared with that for the growth of the encephalon, it is quite evident that the growth is more rapid in the central nervous system than in the body at large, and that it is almost completed in the former at the end of the eighth year, whereas the body has reached but one-third of the weight which it will attain at maturity.

A causal relation between a well-developed central system and the subsequent growth of the entire body is thus suggested, and also it is evident that conditions which influence growth will at any time find the body on the one hand, and the central system on the other, at quite different phases in their development.

The long-continued growth of the body brings it about that the central system, which at birth may form 12 per cent. of the total weight of the individual, is at maturity about 2 per cent. or less. For this change in proportion the increase of the muscular system is mainly responsible.

Further, the much smaller mass of the muscular system in the female is the chief cause of the higher percentage value of the central system in the female—a relation which has been much emphasized, but which is really not significant, since in both sexes this high percentage value of the central system is most developed at birth, and becomes steadily less marked as maturity is approached.

Increase in the Number of Functional Nerve-elements.—Having thus briefly indicated the facts of growth so far as they can be detected by the balances, it still remains to mention the series of changes which may be studied by other means, such as micrometric measurements or enumeration. The results obtained by these methods are somewhat complex and must be treated with great care. Human embryology indicates that after the third month of fetal life the number of cells in the central system is not increased. With the cessation in the production of new cells the only remaining means of increase in size is by enlargement of those cells already present.

How this occurs is well indicated by the accompanying table (page 728), which shows the change in the size of cell-bodies in a given locality in man.

All vertebrates are not similar in respect to the manner of this change. Birge[1] has shown that in frogs there is a gradual increase in the number of the fibres forming the ventral and dorsal spinal roots, and that this goes on at the rate of about fifty additional fibres in the ventral roots and seventy in the dorsal, for each gram added to the total weight of the frog. The increase was still apparent in a frog weighing one hundred and twelve grams. In the case of the ventral root-fibres it was also determined that the cells of origin in the ventral horns of the spinal cord increased in number in a similar manner. Here is exemplified an instance of long-continued enlargement of the nervous

[1] Birge: *Archiv für Anatomie und Physiologie*, Supplem., 1882.

system by the regular development of immature cells, a method of growth most marked probably in those animals which increase in size so long as they live.

Volumes of the Largest Cell-bodies in the Ventral Horn of the Cervical Cord of Man (based on Kaiser's records of the mean diameters).

The volume $700\mu^3$, in the fetus of four weeks, is taken from His, and the figures represent multiples of that volume.

Subject.	Age.	Proportional volume of the cell-bodies $1=700\mu^3$.	Time interval.
Fetus	4 weeks	1 ⎫	
"	20 "	17 ⎪	
"	24 "	31 ⎬	36 weeks.
"	28 "	67 ⎪	
"	36 "	81 ⎭	
Child at birth	—	124 ⎫	
Boy at fifteen years	—	124 ⎬	15 years.
Man, adult	—	160	15 "

It is believed that in this case the *new* cells and *new* fibres are not, strictly speaking, new morphological elements, but are the result of developmental changes taking place in the cells present in the system from an early period.

A distinction is thus to be made between cell-elements which, because they are not developed, are therefore not a part of the system already physiologically active, and those cells already organized together and which are fully functional. When, therefore, it is said that the cells of origin for the ventral root-fibres increase in number, the increase refers to the latter group, and not to the total number of elements of both kinds present in the cord. In other words, the number of cells appears to increase because the number of developed cells become greater.

On the other hand, Schiller[1] counted the number of nerve-fibres in the oculo-motor nerves of cats, and found but a very slight difference in this number between birth and maturity. So far, then, as this nerve is concerned, it is found in the cat to be nearly complete at the time of birth.

In man there are very few observations on the increase in the number of functional nerve-cells with age. Kaiser,[2] as is shown in the accompanying table, found in man increasing numbers of large nerve-cells in the ventral horns of the spinal cord at the ages named:

Number of Developed Cells in the Cervical Enlargement of Man at Different Ages (Kaiser).

Age.	Number of Nerve-cells.
Fetus, 16 weeks	50,500
" 32 "	118,330
New-born child	104,270
Boy, fifteen years	211,800
Male, adult	221,200

[1] Schiller: *Comptes rendus de l'Académie des Sciences*, Paris, 1889.
[2] *Die Functionen der Ganglienzellen des Halsmarkes*, Haag, 1891.

Here, as in the frog, the apparent increase must be looked upon as due to the gradual development of elements present from an early date.

Increase in the Fibres of the Cortex.—The area of the cerebral cortex (see Fig. 205) varies according to several conditions, but in general the more voluminous the cerebral hemispheres the greater its extent. That which covers the walls of the sulci has in man about twice the extent of that directly exposed on the surface of the hemispheres.
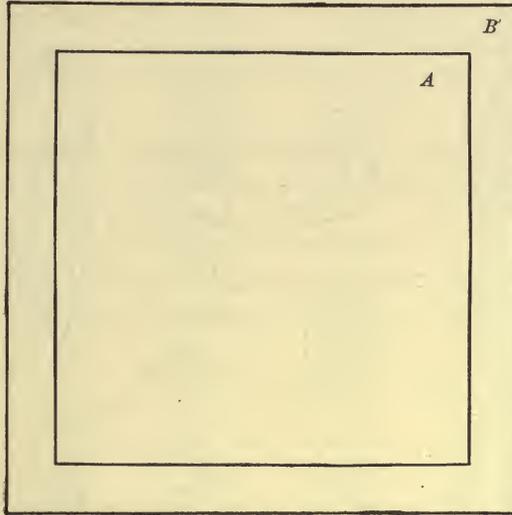
Fig. 205.—Diagram illustrating the extent of the cerebral cortex. The outer square (*B*) shows a surface one-twenty-fifth of 2352 sq. cm. in extent; the inner square (*A*) has two-thirds of this area, and is the proportion of the cortex sunken in the fissures. 2352 sq. cm. is approximately the area of the entire cortex in a male brain weighing 1360 grams.

In the cortex of the human cerebral hemispheres it has been shown by Vulpius[1] that the number of fibres in the different layers is greater at the thirty-third year than at earlier periods, and in old age the number is again decreased. At exactly what age decrease sets in is not to be determined from these observations. They show, simply, that in general the number of fibres was less at seventy-nine years than at thirty-three years.

In a similar way Kaes[2] has compared the development of the thickness of the cortical fibre-layers in a youth of eighteen years as contrasted with a man of thirty-eight years, and found them thicker in the latter.

The relation of the cell-bodies in the cerebral cortex at different ages is illustrated by Figure 206.

Significance of Medullation.—Two sorts of nerve-fibres are described— those with and those without a medullary sheath. Both have the power of isolated conduction, but in the peripheral system the non-medullated fibres are found in connection with the sympathetic system, where less specialized functions are carried on, and also in a large but varying degree in the central sys-

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[1] Vulpius: *Archiv für Psychiatrie und Nervenkrankheiten*, 1892.
[2] *Neurologische Centralblatt*, 1891.

tem. The wider significance of this difference in medullation is at the moment quite obscure.

The first suggestion, that absence of the medullary sheath is an immature condition which persists in various parts of the nervous system, brings us at
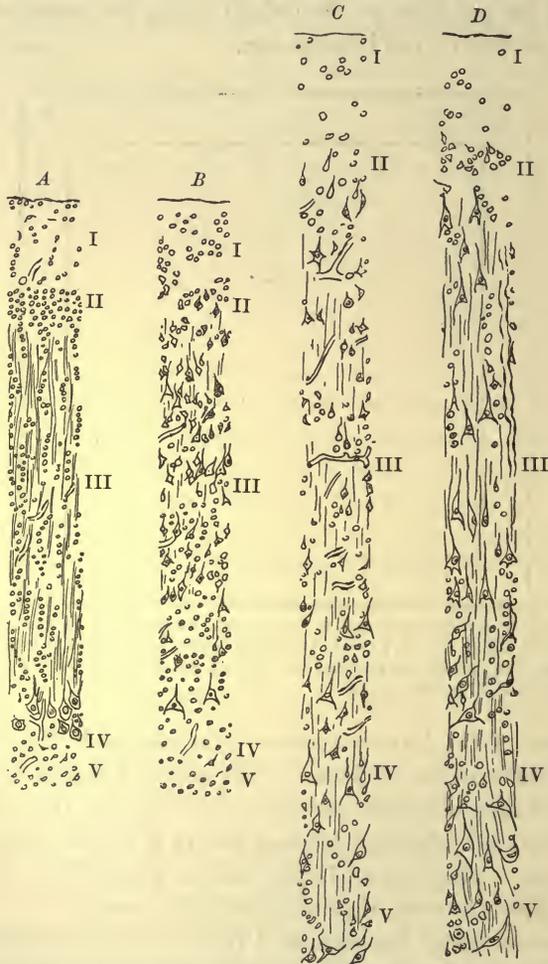
FIG. 206.—To show in the developing human cortex the increase in the number and size of the mature cell-bodies, as well as the separation of them from one another (Vignal): *A*, fetus of twenty-eight weeks; *B*, fetus of thirty-two weeks; *C*, child at birth; *D*, man at maturity; I–V, layers of the cortex according to the enumeration of Meynert.

once to the question of the physiological difference thus implied but not explained.

It is known that the central system is at birth very imperfectly medullated, and the growth of these medullary sheaths must form a large part of the total increase in its bulk. In the mature fibre the axis-cylinder and the medullary sheath have nearly equal volumes, and therefore approximately equal weights. The medullated fibres form probably not less than 90 per cent. of the total

weight of the nerve-tissues composing the encephalon, and of this one-half would be medullary substance.

Increase in the Mass of Nerve-cells.—The amount of this increase under various conditions has already been discussed, and been found to range between zero and fifty-thousand-fold.

Number of Cells.—A conservative estimate of the number of cells in the entire central system is 3,000,000,000. Giving each cell of this number a volume of at least $700\mu^3$ (His' measurements give $697\mu^3$), then this entire number could easily be placed in 2.25 cu.cm. We assume that about three-quarters of the total volume of the central system is nerve-tissue proper, while the remaining quarter is composed of the supporting tissues and blood-vessels.

Volume of Central System.—The volume of the entire system containing cells of the number and size chosen, as well as the supporting tissues, would then, on the supposition made, be about 3 cu.cm., which is approximately that found in the human fetus at the end of the twelfth week (see Fig. 207). The enlargement occurring between this time and maturity is that between 3 cu.cm. and 1340 cu.cm., the latter figure being the volume of the encephalon and cord,
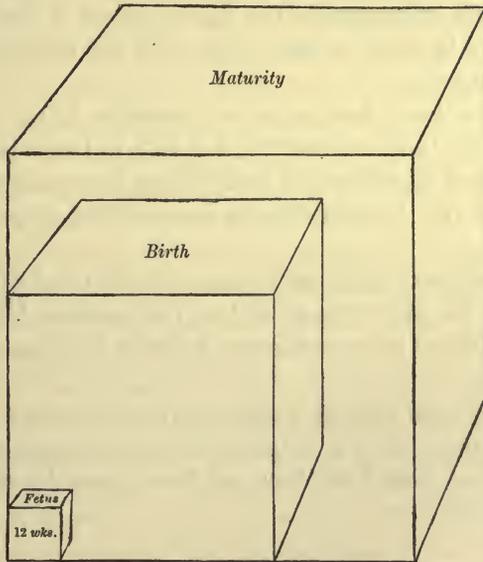
Fig. 207.—Cubes illustrating the relative volumes of the central nervous system at the twelfth week of fetal life, at birth, and at maturity. The cubes as shown have exactly one-eighth of their true volumes.

weighing 1386 grams (encephalon 1360 grams, and spinal cord 26 grams), and having together a specific gravity of 1036. This change demands an average enlargement in the nerve-elements of four hundred and forty-seven-fold, which, it is seen, is well within the limits of that found for a cortical cell of medium size which had enlarged six hundred and sixty times (pages 608, 609).

Estimates of the Volume of the Central Nervous System. Encephalon and Spinal Cord at Different Ages.

Three-quarters of this volume is assumed to represent the nerve-elements proper. For the first two records I am indebted to Professor F. P. Mall. The third is estimated.

Subject.	Age.	Weight.	Volume of Nervous System— Encephalon and Cord.	
		Grams.	Vol., cu.cm.	¾ of this in cu.cm.
Fetus	2 weeks.	—	0.04	0.03
"	4 "	—	0.2	0.15
"	12 "	—	3.0	2.25
Child	At birth.	381+4 385	376	282
Man	Adult.	1360+26 1386	1340	1005

From the foregoing facts, together with those bearing on the cell-elements, it is possible to get some conception of the growth-processes in the central system, and to see how they are due to an enlargement of the nerve-elements which have been formed at a very early stage in the life-history of the individual. In such enlargements the chief increase is due to the formation of the neurons, and in them, in turn, about half the substance is represented by the medullary sheaths.

In all probability these sheaths are no exception to the rule according to which all parts of the body are variable, not only in their absolute but also in their relative size, and therefore it is possible that the quantitative variation in this constituent is a very important factor in modifying the weight of the central system.

Change in Specific Gravity with Age.—During fetal life and at birth the specific gravity of the nerve-tissues is low, but becomes higher at maturity. This change is correlated in some measure with the development of the medullary substance.

For the gross physical changes which have thus been indicated as occurring during growth an explanation is to be found in the changes affecting the constituent elements, and these have been set forth when describing the growth of the individual cells.

C. Organization and Nutrition of the Central Nervous System.

What is here meant by organization may be easily illustrated. When, for example, by later growth new tissue is added to the liver or the skin is increased in area or a muscle enlarged, there is caused by the addition of new substance a change in the powers of these tissues, which is mainly quantitative. The larger organ exhibits the same capabilities that the smaller organ exhibited, but does so in a greater degree.

In the central nervous system, on the other hand, it appears that with

growth the system becomes capable of new reactions in the sense that its various responses are controlled and directed by a larger number of incoming impulses, and thus the number, complexity, and refinement of the reactions is increased, and in this sense it really attains new powers.

With the change in the age of the central system there occurs from birth to maturity, if we may judge from general reactions, an increase in this organization which is maintained during the prime of life, and then in old age this breaks down, at first gradually, and later rapidly. It becomes important, therefore, to examine the manner in which this organization is accomplished.

Organization in the Central System.—When first formed the cells composing the central system are completely separated from one another. In the mature nervous system the impulses, as has been pointed out, probably travel for the most part from the neurons of one unit to the dendrons of another. From the original position in which the young cells, the neuroblasts, are produced, they plainly migrate, and often these migrations involve groups of cells, as in the case of those forming the olivary bodies (His).

For organization the most important changes, however, are those affecting the branches, both dendrons and neuron. During growth both of these increase in the length of their main stem and of their respective branches. In picturing the approach of two elements within the central system the process is usually described as that of the outgrowth of the neuron toward the dendrons or bodies of those cells which are destined to receive the impulse, but it must by no means be forgotten that the dendrons are also growing, and the question of the approximation of the branches of these latter to those of the neurons depends on their own activities as well.

The conditions modifying this process are, however, obscure. It is evident that medullation outside of the central system is not necessary to the functional activity of a fibre, and therefore probably in the central system unmedullated fibres are also in many cases functional. Whatever may be the relation of the establishment of new pathways to the acquisition of medullary sheaths by the neuron and its branches, it is also clear that all fibres which when mature are medullated begin as unmedullated fibres, that the increase in medullation throughout the central system is an index of the increase in organization. A consideration of the facts of growth in the layers of the cortex, for instance, will show them to be open to this interpretation.

Applying these ideas concerning organization to the three classes of cells, afferent, central, and efferent, composing the nervous system, we find the following : In the central system the afferent cells contribute to organization by the multiplication of the collaterals. At the periphery the division of the branches of the neuron increases the number of opportunities for excitation which such an element offers. These cells are without dendrons. Among the central cells all possible modes of growth are contributory; that is, the branches of both kinds add directly to the complexity of the central pathways. On the other hand, the efferent group contributes to this com-

plexity almost solely by the formation of dendrons, the collaterals which come from the neurons of these cells forming but an insignificant contribution. Not only, therefore, is organization in large part dependent on changes in the central cells by reason of their numerical preponderance, but also by reason of the fact that to them a multiplication of pathways both by elaboration of the neurons and the dendrons is alone possible.

Defective Development.—In view of these facts, defective development in the nervous system may depend on failure in one or more of these several processes by which the system is organized, and it should be possible to correlate defective development involving mainly one set of elements with a distinct clinical picture. The results of defective development are not merely an absence of certain powers, but in some measure a diminution in the strength and range of those that remain.

Laboratory Animals.—The bearing of these facts on the conception which we form of the nervous systems of those animals commonly employed for laboratory experiments may be here mentioned. The frog, pigeon, rabbit, cat, and dog form a series in which the total mass of the central system increases from the beginning to the end of the series.

The number of cells in the largest system, that of the dog, is many times greater than that in the smallest, the frog, and it is probable that the others are in this respect intermediate. Organization is apparently more rapidly completed and more nearly simultaneous throughout the entire system in forms like the frog and pigeon, and also in these latter the organization is least elaborate at the cephalic end. While the educability of the nervous system of the dog may depend on several conditions, the comparative slowness of organization is undoubtedly one of them, and a very important one. Where the organization is early established it is found that the parts organized have a greater independence than under the reverse conditions. In selecting an animal, therefore, on which to make a series of experiments, these several facts must be kept in view, for the choice is by no means a matter of indifference.

Blood-supply.—For the general distribution of the blood-vessels in relation to the gross subdivision of the brain the student is referred to the works on anatomy. The finest network of vessels is, however, to be found where the cell-bodies are most densely congregated, and indeed the distinction between the masses of gray and white matter in the central system is as clearly marked by the relative closeness of the capillary network as in any other way. One result of this relation between the blood-supply and the cell-bodies which form the gray matter is a general arrangement of the vessels along the radii of the larger subdivisions of the brain, as the cerebral hemispheres and the cerebellum.

The conditions which control the circulation within the cranium and spinal canal are not exactly the same at all periods of life, but the variations occur in minor points only.

The general conditions are the following: The evidence, physiological and

histological, is against the existence of vaso-motor nerves in the vessels of the pia or of the encephalon and cord (see Circulation).[1]

The circulation in these regions, therefore, is not modified by any *reflex* variations in the calibre of the vessels. The authors just cited do not find any evidence for a local control of the arterioles whereby the products of nerve-cell activity cause an increase in the diameter of the vessels affected by these substances. The reactions of the central vessels are broadly those of a system of elastic tubes in a closed cavity. As a result, it is found that the *quantity* of blood in the central system is subject to *very slight variations only*. A rise in the arterial pressure causes a more *rapid* flow of the blood through the encephalon. It also causes a rise in the venous pressure, and with this a corresponding rise in the intracranial pressure, the last two varying in the same sense and to the same extent.

The flow through the central system is subject to the influence of gravity, and takes place the more readily the more the resistance is diminished.[2] The principal controlling mechanism is in the splanchnic area. According to the condition of the vessels in this area the intracranial blood-pressure varies.

It is to be noted in passing that when a person lying on a table is balanced on a transverse axis, this axis is about 8.77 centimeters to the cephalic side of the line which joins the heads of the femurs.[3] This leaves, of course, the splanchnic area mainly on the cephalic side of this axis, and hence any inflow of blood from the extremities would tend to make the head end of the person thus balanced dip down. This dip will occur even when the splanchnic area alone is filled, and hence the dipping as such would not *necessarily* indicate an increase in the quantity of blood in the encephalon.

In the adult the cranial cavity is almost rigidly closed. There is an opportunity for the escape of a small quantity of fluid through the foramen magnum into the vertebral canal. When, as the result of increased arterial pressure, the brain has increased so as to drive out the subdural fluid, the brain is forced against the walls of the cranium and blocks the outflow into the spinal canal. In the same way it has been found that if a mass displacing from 2–3 cu.cm. be introduced into the subdural space of a dog the brain will adjust itself without rise of intracranial pressure. If in this case the volume of the mass introduced is increased, there follows a rise of intracranial pressure, and this rise in every instance tends to impede the circulation through the brain. While the fontanelles are open the brain normally pulsates, and we recognize in its variations in volume all the different variations in blood-pressure with which we are familiar. The pulsation of the brain is doubtless an important aid to the movements of the fluids within and hence tends to facilitate nutrition during the earlier periods of growth.

In pathological cases where the cranial wall has been destroyed, there is a similar variation in volume to be observed in the adult, and it is possible

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[1] Bayliss, Hill, and Gulland: *Journal of Physiology*, 1895, vol. xviii.
[2] Hill: *Journal of Physiology*, 1895, vol. xviii.
[3] W. und Ed. Weber: *Mechanik der menschlichen Gehwerkzeuge*, 1836.

that the beneficial effects which in so many instances follow trephining of the skull may depend upon this mechanical release. Of course in cases with a defective skull-wall an increase in arterial pressure causes a more decided increase in the *volume* of blood in the brain; this, however, is much more marked than it would be under ordinary conditions, and is not to be regarded as the main effect, which is an increase in the quantity of the blood passed through the central system in a unit of time. Mosso[1] has found the temperature of the blood coming from the brain (dogs) slightly higher than that of the rectum and of the arterial blood. The differences are very small, but he draws the conclusion that the metabolic processes in the brain are sufficiently intense to *raise* the temperature of the blood passing through it.

As against the intensity of the metabolism in the central system, it has been observed that blood taken from the torcular Herophili of the dog was intermediate between arterial blood and that taken from the femoral vein, thus indicating that the arterial exchange was less intense in the brain than in the muscles of the leg. The following is a condensed statement of the figures:

Percentages of Oxygen and Carbonic Acid in various Samples of Dogs' Blood (Hill).[2]

Average of 52 arterial samples	CO_2	37.64 per cent.
	O	18.25 "
Average of 42 torcular samples	CO_2	41.65 "
	O	13.49 "
Average of 28 femoral vein	CO_2	45.75 "
	O	6.34 "

The absolute quantity of blood in the brain and cord is certainly small; if we may judge from the observations on animals, it is not more than 1 per cent. of the entire blood in the body. It is to be remembered, however, that the cell-bodies, which alone are well supplied with blood, probably represent less than one-tenth of the entire encephalic mass.

With general rise and fall of pressure elsewhere there is a rise and fall of pressure within the central system. During the first phases of mental activity blood is withdrawn from the limbs; the blood thus withdrawn can be shown to pass toward the trunk, for when a person lying on a horizontal table supported at the centre on a transverse knife-edge is just balanced, then increased activity of the cerebral centres causes the head end to dip down (Mosso), and if the skull wall is defective the brain is seen to swell.

In the latter stages of fatigue the blood-supply to the nerve-centres diminishes owing to a decrease in force of the heart-beat and the tonicity of the splanchnic vessels, so that the brain in birds exhausted by a long flight has been found by Mosso to be in a high degree anæmic. There is much reason to think that in man a similar reaction occurs.

The study of the cerebral circulation in the case of those in whom the skull-wall is at some point deficient shows a bulging of the skin over the opening into the cranial cavity as a result of mental effort or emotion. In the

[1] *Die Temperatur des Gehirns*, 1894, Leipzig.   [2] *Journal of Physiology*, vol. xviii., 1895.

normal adult this bulging cannot of course occur to anything like such an extent, and the space for the arterial blood must be gained in the first instance by driving out the blood from the venous sinuses within the cranium and through the removal of the subdural fluid.

Influence of Glands.—In the growth of the nervous system it is not only the quantity, but the peculiar qualities, of the blood that are important, and among the various glands the activity of which is necessary for the growth of the nervous, as well as the other systems, and also needed for its full maintenance, the thyroid appears as very important. In sporadic cretinism, associated as it is with atrophy of the thyroid, the feeding of sheep's thyroids has produced remarkable growth-changes in all parts of the body—the nervous system included.

At the same time, experimental extirpation of the thyroid is followed by destructive changes in the central system, caused by disturbances in its nutrition.

Starvation.—In starving animals the nervous system loses but very little in weight.[1] This small loss is most striking, and would seem to be best explained on the assumption that the other tissues are used to keep up the central system, which, when even slightly reduced in weight, ceases to act.

Fatigue.—The histological basis of fatigue, as expressed by the changes in the individual cells, has already been discussed. The fatigue of the system as a whole is but the expression of fatigue in large numbers of its elements, but the manner in which the changes show themselves is somewhat complicated.

When the attempt is made to raise a weight by the voluntary contractions of the muscles of the index finger at regular intervals, say once a second, it is found that if the weight be heavy the power of the finger decreases, and the
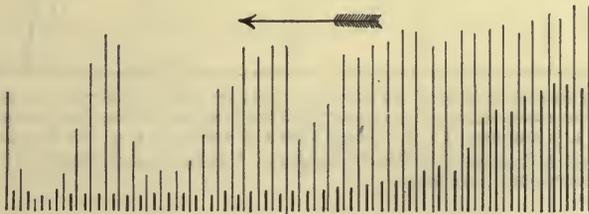
Fig. 208.—A record of the extent of the flexions of the forefinger lifting a weight at regular intervals. The light lines are those for the voluntary contractions; the heavy lines, those for contractions following the direct stimulation of the flexor muscles by electricity. In the former there are periods, in the latter none. The arrow shows the direction in which the record is to be read (Lombard).

weight soon ceases to be lifted as high as at first. Finally, a point is reached when the voluntary effort produces little or no elevation of the weight. If, however, despite this failure, the effort is still made at regular intervals, it occurs in some persons that this power returns gradually, and a few seconds later the contractions are very nearly as high as at the beginning of the experiment (Mosso). This phenomenon may repeat itself many times, giving a record formed by groups of contractions most extensive near the centre of

[1] Voit : *Zeitschrift für Biologie*, Bd. xxx., 1894.

each group, these latter being separated by portions of the curve in which the contractions are very small or wanting (see Fig. 208). (See General Physiology of Nerve and Muscle, p. 126.)

Daily Rhythms.—Within the cycle of the astronomical day the progress of events leading to fatigue is not a steady one. Lombard[1] found that if the capacity for voluntary effort was measured by the amount of work which could be done by voluntarily contracting the flexor muscles of the index finger *before the first failure* to respond to a voluntary stimulus appeared, then the curve
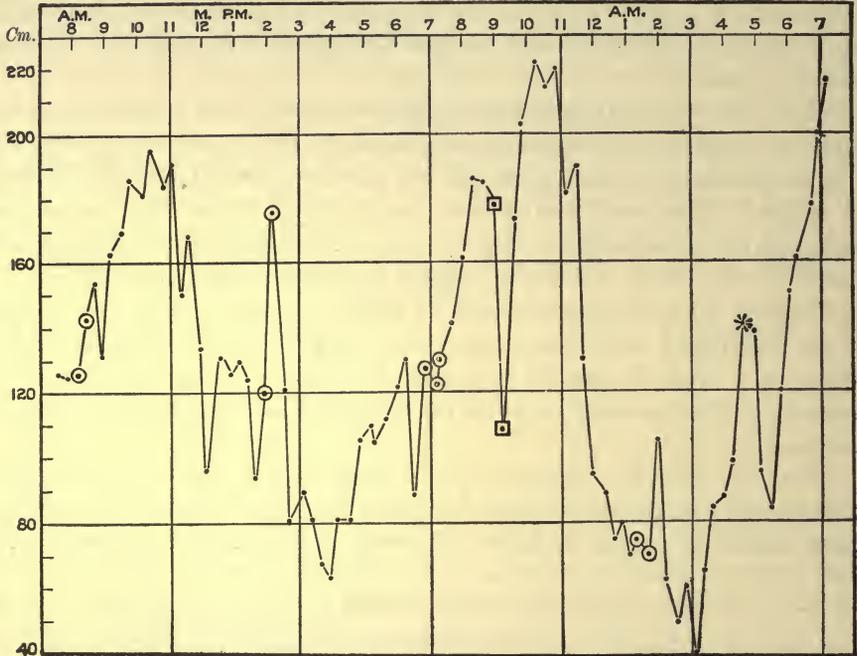
Fig. 209.—Showing at each hour of the day and night how many centimeters a weight of 3000 grams could be raised by repeated voluntary contractions of the forefinger before fatigue set in. The curve is highest at 10 to 11 A. M. and 10 to 11 P. M.; lowest, 3 to 4 P. M. and 3 to 4 A. M. Circle with dot, observation made just after taking food; square with dot, smoking; *, work done eight minutes after drinking 15 cubic centimeters of whisky (Lombard).

expressing this capacity for voluntary work throughout the day was represented as in Fig. 209. Briefly, the curve shows two maxima, at 10 P. M. and 10 A. M., with two minima midway between them. In general the immediate effect of taking food is to increase the work done by the subject. Alcohol has the same effect, while smoking produces a decrease.

Further, from day to day this capacity for work was influenced by a number of external conditions—temperature, barometric pressure, etc.

Time taken in Central Processes.—All processes in the nervous system take time, and are for the most part easy to measure. The rate of the nerve-impulse has already been given. It has also been noted that in passing through the body of a spinal ganglion-cell the impulse suffers some delay. When,

[1] *Journal of Physiology*, vol. xiii., 1892.

however, it passes from one element to another the delay is even more marked, and it is plausible to assume that this detention occurs at the juncture of the elements. Thus in those parts of the central system where the cell-elements and also the cell-junctions are most numerous, the time taken is longest.
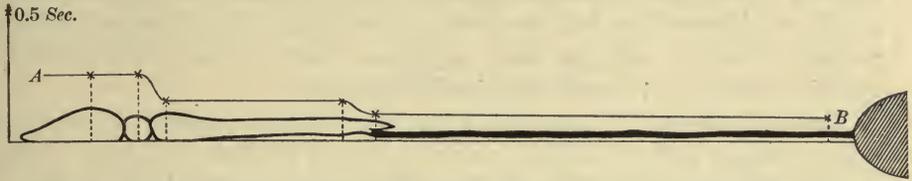
FIG. 210.—To show the rate at which impulses pass through the nervous system of a frog. At the extreme left the vertical has the value of 0.5 second and the other verticals are compared with it; thus between the cerebrum and the optic lobe requires about 0.25 second; between the bulb and the lumbar enlargement a greater distance—only about half the time; and for the still greater distance represented by the length of the sciatic nerve even less time is needed (Exner).

Figure 210 shows this very well. Between the middle of the cerebral hemisphere and the optic lobe, although the distance is short, the impulse takes twice as long to travel as between the bulb and the lumbar enlargement. When this time is measured in the conscious individual it is of course open to a long series of modifying conditions, and these appear to be in part the same conditions which modify the muscular endurance of the individual at different portions of the day. Thus it has been determined that the speed with which reactions can be made, as indicated by the reaction time, is subject to variations, and does not steadily decrease from the morning to the evening.

It has been the purpose of the paragraphs just preceding to indicate that through the day it is not possible to demonstrate a steady decline of power in the nervous system. We begin the morning, to be sure, feeling fresh, and are fagged in the evening, but the course by which this condition has been attained is not a simple or direct one.

D. Sleep.

Conditions Favoring Sleep.—To recover from fatigue sleep is required. The prime condition favoring sleep is the diminution of nerve-impulses passing through the central system. This is accomplished in two ways. In the first instance it is usual to reduce all incoming stimuli to a minimum. This is most directly under our own control. On the other hand, the permeability of the nervous system and the intensity with which it responds are decreased as the result of the beginning fatigue. How these conditions are brought about has been a matter of much speculation and some experiment.

The parts played by the sensory and that by the central cells vary somewhat at different times of life, for impulses are much less widely diffused in the early years than at maturity. Moreover, in childhood the amount of stored material is small, large at maturity, and small again in old age, and this holds true for all the groups of cells. Hence the cells would, by reason of this fact, have the greatest capability for work in the middle period.

Between childhood and old age there is, however, this difference—that while in the former the non-available substances in the cell are developing, not yet having matured, those in the latter have in some way become permanently useless. The degree to which the blood-supply can be controlled varies with age, and the amounts of substance capable of yielding energy at various periods of life are different; so that, considering these factors alone, though there are probably others, it may be easily appreciated that the sleep of childhood, maturity, and old age should be quite distinguishable.

Cause of Sleep.—It is recognized that local exercise is capable of producing general fatigue, and the fatigued portions give rise to afferent impulses which, reaching the central system, cause some of the sensations of fatigue; moreover, the active tissues (nerve-cells and muscles) yield as the result of their activity some by-product which is carried by the blood through the central system and becomes the chief cause of sleep. It has been shown by Mosso that if a dog be thoroughly fatigued, giving all the signs of exhaustion, and the blood from this dog be transfused to one that has been at rest, after the transfusion the dog which has received the blood from the exhausted animal will exhibit the symptoms of fatigue in full force. The inference is that from the tired animal certain by-products have thus been transferred, and that these are responsible for the reactions. We know, further, that we can distinguish in ourselves different forms of the feeling of fatigue, and that the sensations which follow the prolonged exercise of the muscular system differ from those following the exercise of the higher nerve-centres.

Cessation of stimuli, decreased responsiveness of the active tissues, and a change in the composition of the blood are the preliminaries to sleep. To these should be added the diminution of the blood-supply to the head.

A condition superficially resembling sleep can be induced in various ways. Removal of all external stimuli, extreme cold, anæsthetics, hypnotic suggestion, compression of the carotids, a blow on the head, loss of blood, all produce a state of unconsciousness which, in so far, has a similitude with sleep. These conditions produce this state, however, by mechanically decreasing the blood-supply or cutting off the peripheral stimuli.

Normal sleep is tested by the fact that during its progress the changes that occur in the central system are recuperative, whereas this feature may be more or less absent from the states which merely resemble it.

Condition of the System during Sleep.—It appears that during sleep the capacity of the central system to react is never lost. Were such the case it would not be possible to awaken the sleeper. Moreover, the sleeping person is far more responsive to stimuli from without than at first might be thought. The close relations between dreams and external stimuli has been recognized, and plethysmographic studies show still more clearly how the matter stands.

It was found that when a subject fell asleep with the arm in a plethysmograph various stimuli which did not waken the sleeper still served to cause a diminution in the volume of the arm, which was certainly due to the with-

drawal of blood from it, the blood-supply to the brain being probably at the same time increased (see Fig. 211).

FIG. 211.—Plethysmographic record taken from the arm of a person sleeping in the laboratory. A fall in the curve indicates a decrease in the volume of the arm. The curve is to be read in the direction of the arrow. 1, the night watchman entering the laboratory, waking the subject, who shortly fell asleep again; 2, the watchman spoke; 3, watchman went out; these changes (2 and 3) occurred without awakening the subject (from experiments made by Messrs. Bardeen and Nichols, Johns Hopkins Medical School).

This experiment shows that during sleep the nervous system is capable of reactions which are not remembered in any way, but which naturally form a feature of the condition intermediate between waking and deep slumber. The depth of sleep as determined by the strength of the stimulus necessary to elicit an efficient response has been measured. The stimulus in these experiments was the sound caused by the fall of a ball upon a plate, and the measure was
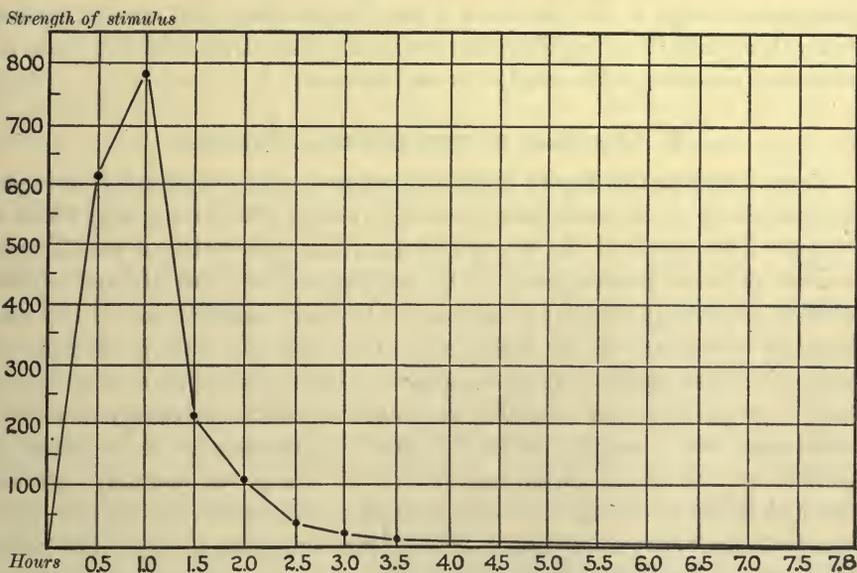
FIG. 212.—Curve illustrating the strength of an auditory stimulus (a ball falling from a height) necessary to waken a sleeping person. The hours marked below. The tests were made at half-hour intervals. The curve indicates that the distance through which the ball required to be dropped increased during the first hour, and then diminished, at first very rapidly, then slowly (Kohlschütter).

the height from which the ball must fall in order to produce a sound loud enough to awaken a sleeping person. The results of the observations are shown in Figure 212.

It is seen from this that the period of deep slumber is short, less than two hours, and is followed by a long period, that of an average night's rest, during which a comparatively slight stimulus is sufficient to awaken. Almost the same results have been more recently obtained by Mönninghoff and Piesbergen.[1]

It is evident that the effectiveness of such a stimulus is, however, no measure of the recuperative processes in the central system. Repair is by no means accomplished during the interval of deep sleep, and experience has shown, as in the case of persons undertaking to walk a thousand miles in one thousand hours, that although such an arrangement left the subject with two-thirds of the total time for rest and refreshment, yet the feat was most difficult to accomplish by reason of the discontinuity in the sleep. The changes leading to recuperation needed longer periods than those permitted by the conditions of the experiment.

Loss of Sleep.—Loss of sleep is more damaging to the organism as a whole than is starvation. It has been found (Manáceine) that in young dogs which can recover from starvation extending over twenty days, loss of sleep for five days or more was fatal. Toward the end of such a period the body-temperature may fall as much as 8° C. below the normal and the reflexes disappear. The red blood-corpuscles are first diminished in number, to be finally increased during the last two days, when the animal refuses food. The most widespread change in the tissues is a fatty degeneration, and in the nervous system there were found capillary hemorrhages in the cerebral hemispheres, the spinal cord appearing abnormally dry and anæmic.

E. Old Age of the Central System.

Metabolism in the Nerve-cells.—Connected closely with fatigue are those alterations both of the constituent nerve-cells and of the entire system found in old age. The picture of the changes in the living cells is that of anabolic and katabolic processes always going on, but varying in their absolute and relative intensity according to several conditions. Of these conditions one of the most important is the age of the individual. In youth and during the growing period of life the anabolic changes appear within the daily cycle of activity and repose to overbalance the katabolic, the total expenditure of energy increasing toward maturity. During middle life the two processes are more nearly in equilibrium, though the total expenditure of energy is probably greatest then, and finally in old age the total expenditure diminishes, while at the same time the anabolic processes become less and less competent to repair the waste. The question why in the nervous system the energies wane with advanced age is but the obverse of the question why they wax during the growing period. The essential nature of these changes is in both instances equally obscure.

Decrease in Weight of Brain.—The weight of the brain in advanced life shows that between fifty and sixty years there is a decrease in the bulk of the encephalon in those persons belonging to the classes from which the greater

[1] *Zeitschrift für Biologie*, 1893, Bd. xix.

number of the records have been obtained. So far as can be seen, there is no marked change in the proportional development of the encephalon in old age, save that the waste appears to be slightly greater in the cerebral hemispheres than in the other portions.

Changes in Encephalon.—The thickness of the cerebral cortex diminishes in harmony with the shrinkage of the entire system. In large measure this must depend on the loss of volume in the various fibre-systems, which, according to the observations of Vulpius, show a senile decrease in the number of fibres composing them. This decrease is more marked in the motor than in the sensory areas. The time at which it commences cannot, however, be well judged, owing to the small number of records after the thirty-third year. Where records are made between this and the seventy-ninth year it appears that there is no decided diminution until after the fiftieth year, though at the seventy-ninth the decrease is clearly shown. Engel has shown that the branches of the arbor vitæ of the human cerebellum decrease in size and number in old age.[1]

To the anatomy of the human nervous system in old age contributions have been made by studies on the pathological anatomy of paralysis agitans.[2]

In subjects suffering from this affection the bodies of the nerve-cells are shrunken, pigmented, and show in some cases a granular degeneration; the fibres in part are atrophied and degenerated; the supporting tissues increase, and the walls of the small blood-vessels are thickened. These changes have been found principally in the spinal cord, being most marked in the lumbar region. But the cords of the aged persons who do not exhibit the symptoms of paralysis agitans show similar changes, though usually they are not so evident, and hence the pathological anatomy of this disease resolves itself into a somewhat premature and excessive senility of the central system.

Changes in the Cerebellum.—From the examination of the cerebral cortex in the case of a man dying of old age (Hodge) no peculiarities were determined, but in the cerebellum some cells were shrunken and others (cells of Purkinje) had completely disappeared. In the antennary ganglion of bees a very striking difference appears between those dying of old age and the adult just emerged from its larval skin. These changes are comparable with those described in mammals, and it further appears that in passing from the youngest to the oldest forms cells have disappeared from the ganglia, and that in the young form of the bee there are some twenty-nine cells present for each one found at a later period. Shrinkage, decay, and destruction mark the progress of senescence, and the nervous system as a whole becomes less vigorous in its responses, less capable of repair or extra strain, and less permeable to the nervous impulses that fall upon it; and it thus breaks down, not into the disconnected elements of the fetus, but into groups of elements, so that its capacities are lost in a fragmentary and uneven way.

[1] Engel: *Wiener medicinische Wochenschrift*, 1863.
[2] Ketcher: *Zeitschrift für Heilkunde*, 1892; Redlich: *Jahrbuch für Psychiatrie*, 1893.

XI. THE SPECIAL SENSES.

A. Vision.

The Physiology of Vision.—The eye is the organ by means of which certain vibrations of the luminiferous ether are enabled to affect our consciousness, producing the sensation which we call "light." Hence the essential part of an organ of vision is a substance or an apparatus which, on the one hand, is of a nature to be stimulated by waves of light, and, on the other, is so connected with a nerve that its activity causes nerve-impulses to be transmitted to the nerve-centres. Any animal in which a portion of the ectoderm is thus differentiated and connected may be said to possess an eye—*i. e.* an organ through which the animal may consciously or unconsciously react to the existence of light around it.[1] But the human eye, as well as that of all the higher animals, not only informs us of the existence of light, but enables us to form correct ideas of the direction from which the light comes and of the form, color, and distance of the luminous body. To accomplish this result the substance sensitive to light must form a part of a complicated piece of apparatus capable of very varied adjustments. The eye is, in other words, an optical instrument, and its description, like that of all optical instruments, includes a consideration of its mechanical adjustments and of its refracting media.

Mechanical Movements.—The first point to be observed in studying the movements of the eye is that they are essentially those of a ball-and-socket joint, the globe of the eye revolving freely in the socket formed by the capsule of Tenon through a horizontal angle of almost 88° and a vertical angle of about 80°. The centre of rotation of the eye (which is not, however, an absolutely fixed point) does not coincide with the centre of the eyeball, but lies a little behind it. It is rather farther forward in hypermetropic than in myopic eyes. The movements of the eye, especially those in a horizontal direction, are supplemented by the movements of the head upon the shoulders. The combined eye and head movements are in most persons sufficiently extensive to enable the individual, without any movement of the body, to receive upon the lateral portion of the retina the image of an object directly behind his back. The rotation of the eye in the socket is of course easiest and most extensive when the eyeball has an approximately spherical shape, as in the normal or emmetropic eye. When the antero-posterior diameter is very much longer than those

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[1] In certain of the lower orders of animals no local differentiations seem to have occurred, and the whole surface of the body appears to be obscurely sensitive to light. See Nagel: *Der Lichtsinn augenloser Thiere*, Jena, 1896.

at right angles to it, as in extremely myopic or short-sighted eyes, the rotation of the eyeball may be considerably limited in its extent. In addition to the movements of rotation round a centre situated in the axis of vision, the eyeball may be moved forward and backward in the socket to the extent of about one millimeter. This movement may be observed whenever the eyelids are widely opened, and is supposed to be effected by the simultaneous contraction of both the oblique muscles. A slight lateral movement has also been described.

The movements of the eye will be best understood when considered as referred to three axes at right angles to each other and passing through the centre of rotation of the eye. The first of these axes, which may be called the longitudinal axis, is best described as coinciding with the axis of vision when, with head erect, we look straight forward to the distant horizon; the second, or transverse, axis is defined as a line passing through the centres of rotation of the two eyes; and the third, or vertical, axis is a vertical line necessarily perpendicular to the other two and also passing through the centre of rotation. When the axis of vision coincides with the longitudinal axis, the eye is said to be in the *primary position*. When it moves from the primary position by revolving around either the transverse or the vertical axis, it is said to assume *secondary positions*. All other positions are called *tertiary* positions, and are reached from the primary position by rotation round an axis which lies in the same plane as the vertical and horizontal axis—*i. e.* in the "equatorial plane" of the eye. When the eye passes from a secondary to a tertiary position, or from one tertiary position to another, the position assumed by the eye is identical with that which it would have had if it had reached it from the primary position by rotation round an axis in the equatorial plane. In other words, every direction of the axis of vision is associated with a fixed position of the whole eye—a condition of the greatest importance for the easy and correct use of the eyes. A rotation of the eye round its antero-posterior axis takes place in connection with certain movements, but authorities differ with regard to the direction and amount of this rotation.

Muscles of the Eye.—The muscles of the eye are six in number—viz: the superior, inferior, internal and external recti, and the superior and inferior oblique. This apparent superfluity of muscles (for four muscles would suffice to turn the eye in any desired direction) is probably of advantage in reducing the amount of muscular exertion required to put the eye into any given position, and thus facilitating the recognition of slight differences of direction, for, according to Fechner's psycho-physic law the smallest perceptible difference in a sensation is proportionate to the total amount of the sensation. Hence if the eye can be brought into a given position by a slight muscular effort, a change from that position will be more easily perceived than if a powerful effort were necessary.

Each of the eye-muscles, acting singly, tends to rotate the eye round an axis which may be called the axis of rotation of that muscle. Now, none of the muscles have axes of rotation lying exactly in the equator of the eye—*i. e.* in a plane passing through the centre of rotation perpendicular to the axis

of vision.[1] But all movements of the eye from the primary position take place, as we have seen, round an axis lying in this plane. Hence all such movements must be produced by more than one muscle, and this circumstance also is probably of advantage in estimating the extent and direction of the movement. In this connection it is interesting to note that the eye-muscles have an exceptionally abundant nerve-supply—a fact which it is natural to associate with their power of extremely delicate adjustment. It has been found by actual count that in the muscles of the human eye each nerve-fibre supplies only two or three muscle-fibres, while in the muscles of the limbs the ratio is as high as 1 to 40–125.[2]

Although each eye has its own supply of muscles and nerves, yet the two eyes are not independent of each other in their movements. The nature of their connections with the nerve-centres is such that only those movements are, as a rule, possible in which both axes of vision remain in the same plane. This condition being fulfilled, the eyes may be together directed to any desired point above, below, or at either side of the observer. The axes may also be converged, as is indeed necessary in looking at near objects, and to facilitate this convergence the internal recti muscles are inserted nearer to the cornea than the other muscles of the eye. Though in the ordinary use of the eyes there is never any occasion to diverge the axes of vision, yet most persons are able to effect a divergence of about four degrees, as shown by their power to overcome the tendency to double vision produced by holding a prism in front of one of the eyes. The nervous mechanism through which this remarkable co-ordination of the muscles of the two eyes is effected, and their motions limited to those which are useful in binocular vision, is not completely understood, but it is supposed to have its seat in part in the tubercula quadrigemina, in connection with the nuclei of origin of the third, fourth, and sixth cranial nerves. Its disturbance by disease, alcoholic intoxication, etc. causes strabismus, confusion, dizziness, and double vision.

A nerve termination sensitive to light, and so arranged that it can be turned in different directions, is sufficient to give information of the direction from which the light comes, for the contraction of the various eye-muscles indicates, through the nerves of muscular sense, the position into which the eye is normally brought in order to best receive the luminous rays, or, in other words, the direction of the luminous body. The eye, however, informs us not only of the direction, but of the form of the object from which the light proceeds; and to understand how this is effected it will be necessary to consider the refracting media of the eye by means of which an optical image of the luminous object is thrown upon the expanded termination of the optic nerve—viz. the retina.

Dioptric Apparatus of the Eye.—For the better comprehension of this portion of the subject a few definitions in elementary optics may be given. A

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[1] The axes of rotation of the internal and external recti, however, deviate but slightly from the equatorial plane.

[2] P. Tergast: "Ueber das Verhältniss von Nerven und Muskeln," *Archiv für mikr. Anat.,* ix. 36–46.

dioptric system in its simplest form consists of two adjacent media which have different indices of refraction and whose surface of separation is the segment of a sphere. A line joining the middle of the segment with the centre of the sphere and prolonged in either direction is called the axis of the system. Let the line *A P B* in Figure 213 represent in section such a spherical surface the
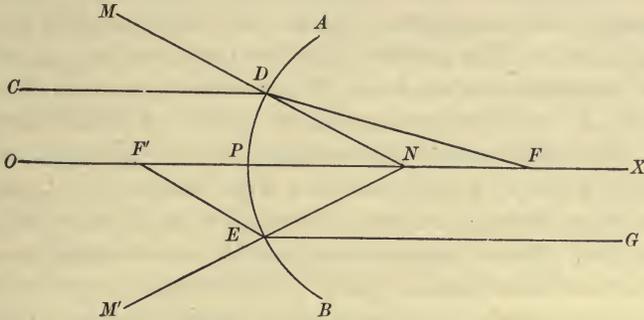
Fig. 213.—Diagram of simple optical system (after Foster).

centre of which is at *N*, the rarer medium being to the left and the denser medium to the right of the line. Any ray of light which, in passing from the rarer to the denser medium, is normal to the spherical surface will be unchanged in its direction—*i. e.* will undergo no refraction. Such rays are represented by the lines *O P*, *M D*, and *M' E*. If a pencil of rays having its origin in the rarer medium at any point in the axis falls upon the spherical surface, there will be one ray—viz. the one which coincides with the axis of the system, which will pass into the second medium unchanged in its direction. This ray is called the *principal ray* (*O P*), and its point of intersection (*P*) with the spherical surface is called the *principal point*. The centre of the sphere (*N*) through which the principal ray necessarily passes is called the *nodal point*. All the other rays in the pencil are refracted toward the principal ray by an amount
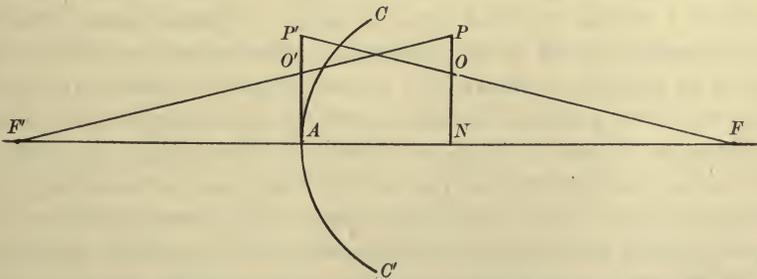
Fig. 214.—Diagram to show method of finding principal foci (Neumann).

which depends, for a given radius of curvature, upon the difference in the refractive power of the media, or, in other words, upon the retardation of light in passing from one medium to the other. If the incident rays have their origin at a point infinitely distant on the axis—*i. e.* if they are parallel to each other—they will all be refracted to a point behind the spherical surface known

as the *principal focus, F.* There is another *principal focus* (*F'*) in front of the spherical surface—viz. the point from which diverging incident rays will be refracted into parallelism on passing the spherical surface, or, in other words, the point at which parallel rays coming from the opposite direction will be brought to a focus. The position of these two principal foci may be determined by the construction shown in Figure 214. Let *C A C'* represent a section of a spherical refracting surface with the axis *A N*, the nodal point *N*, and the principal point *A*. The problem is to find the foci of rays parallel to the axis. Erect perpendiculars at *A* and *N*. Set off on each perpendicular distances *N o*, *N p*, *A o'*, *A p'* proportionate to the rapidity of light in the two media (*e. g.* 2 : 3). The points where the lines *p' o* and *p o'* prolonged will cut the axis are the two principal foci *F* and *F'*—*i. e.* the points at which parallel rays coming from either direction are brought to a focus after passing the spherical refracting surface. If the rays are not parallel, but diverging—*i. e.* coming from an object at a finite distance—the point where the rays will be brought to a focus, or, in other words, the point where the optical image of the luminous object will be formed, may be determined by a construction which combines any two of the three rays whose course is given in the manner above described. Thus in Figure 215 let *A N* be the axis, and *F* and *F'* the principal foci of
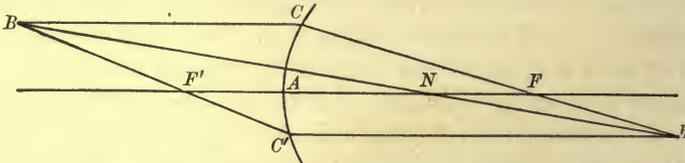
FIG. 215.—Diagram to show method of finding conjugate foci.

the spherical refracting surface *C A C'*, with a nodal point at *N*. Let *B* be the origin of a pencil of rays the focus of which is to be determined. Draw the line *B C* representing the course of an incident ray parallel to the axis. This ray will necessarily be refracted through the focus *F*, its course being represented by the line *C F* and its prolongation. Similarly, the incident ray passing through the focus *F'* and striking the spherical surface at *C'* will, after refraction, be parallel to the axis—*i. e.* it will have the direction *C' b*. The principal ray of the pencil will of course pass through the spherical surface and the nodal point *N* without change of direction. These three rays will come together at the same point *b*, the position of which may be determined by constructing the course of any two of the three. The points *B* and *b* are called conjugate foci, and are related to each other in such a way that an optical image is formed at one point of a luminous object situated at the other. When the rays of light pass through several refracting surfaces in succession their course may be determined by separate calculations for each surface, a process which is much simplified when the surfaces are "centred"—*i. e.* have their centres of curvature lying in the same axis, as is approximately the case in the eye.

Refracting Media of the Eye.—Rays of light in passing through the eye penetrate seven different media and are refracted at seven surfaces. The media

are as follows : layer of tears, cornea, aqueous humor, anterior capsule of lens, lens, posterior capsule of lens, vitreous humor. The surfaces are those which separate the successive media from each other and that which separates the tear layer from the air. For purposes of practical calculation the number of surfaces and media may be reduced to three. In the first place, the layer of tears which moistens the surface of the cornea has the same index of refraction as the aqueous humor. Hence the index of refraction of the cornea may be left out of account, since, having practically parallel surfaces and being bounded on both sides by substances having the same index of refraction, it does not influence the direction of rays of light passing through it. For this same reason objects seen obliquely through a window appear in their true direction, the refraction of the rays of light on entering the glass being equal in amount and opposite in direction to that which occurs in leaving it. For purposes of optical calculation we may, therefore, disregard the refraction of the cornea (which, moreover, does not differ materially from that of the aqueous humor), and imagine the aqueous humor extending forward to the anterior surface of the layer of tears which bathes the corneal epithelium. Furthermore, the capsule of the lens has the same index of refraction as the outer layer of the lens itself, and for optical purposes may be regarded as replaced by it. Hence the optical apparatus of the eye may be regarded as consisting of the following three refracting media : Aqueous humor, index of refraction 1.33 ; lens, average index of refraction 1.45 ; vitreous humor, index of refraction 1.33. The surfaces at which refraction occurs are also three in number : Anterior surface of cornea, radius of curvature 8 millimeters ; anterior surface of lens, radius of curvature 10 millimeters ; posterior surface of lens, radius of curvature 6 millimeters. It will thus be seen that the anterior surface of the lens is less and the posterior surface more convex than the cornea.

To the values of the optical constants of the eye as above given may be added the following : Distance from the anterior surface of the cornea to the anterior surface of the lens, 3.6 millimeters ; distance from the posterior surface of the lens to the retina, 15. millimeters ; thickness of lens, 3.6 millimeters.

The methods usually employed for determining these constants are the following : The indices of refraction of the aqueous and vitreous humor are determined by filling the space between a glass lens and a glass plate with the fresh humor. The aqueous or vitreous humor thus forms a convex or concave lens, from the form and focal distance of which the index can be calculated. Another method consists in placing a thin layer of the medium between the hypothenuse surfaces of two right-angled prisms and determining the angle at which total internal reflection takes place. In the case of the crystalline lens the index is found by determining its focal distance as for an ordinary lens, and solving the equation which expresses the value of the index in terms of radius of curvature and focal distance, thickness, and focal length. The refractive index of the lens increases from the surface toward the centre, a peculiarity which tends to correct the disturbances due to spherical aberration, as well as to increase the refractive power of the lens as a whole.

The curvature of the refracting surfaces of the eye is determined by an instrument known as an ophthalmometer, which measures the size of the reflected image of a known object in the various curved surfaces. The radius of curvature of the surface is determined by the following formula:

$$B : b = A : \frac{r}{2}; \text{ or } r = \frac{2Ab}{B},$$ in which $B =$ the size of the object, $b =$ the size of

the image, $A =$ distance between the object and the reflecting surface, and $r =$ the radius of the reflecting surface. The distances between the various surfaces of the eye are measured on frozen sections of the organ, or can be determined upon the living eye by optical methods too complicated to be here described. It should be borne in mind that the above values of the so-called "optical constants" of the eye are subject to considerable individual variation, and that the statements of authors concerning them are not always consistent.

The refracting surfaces of the eye may be regarded as still further simplified, and a so-called "reduced eye" constructed which is very useful for purposes of optical calculation. This reduced eye, which for optical purposes is the equivalent of the actual eye, is regarded as consisting of a single refracting medium having an index of 1.33, a radius of curvature of 5.017 millimeters, its principal point 2.148 millimeters behind the anterior surface of the cornea, and its nodal point 0.04 millimeter in front of the posterior surface of the lens.[1] The principal foci of the reduced eye are respectively 12.918 millimeters in front of and 22.231 millimeters behind the anterior surface of the cornea. Its optical power is equal to 50.8 dioptries.[2] The position of this imaginary refracting surface is indicated by the dotted line in figure 216. The
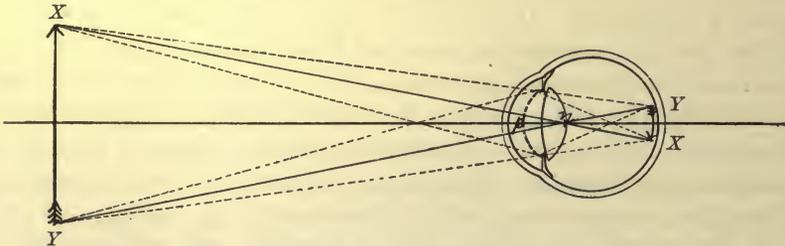
FIG. 216.—Diagram of the formation of a retinal image (after Foster).

nodal point, n, in this construction may be regarded as the crossing-point of all the principal rays which enter the eye, and, as these rays are unchanged in their direction by refraction, it is evident that the image of the point whence they proceed will be formed at the point where they strike the retina. Hence to determine the size and position of the retinal image of any external object— e. g. the arrow in Figure 216—it is only necessary to draw lines from various

[1] Strictly speaking, there are in this imaginary refracting apparatus which is regarded as equivalent to the actual eye two principal and two nodal points, each pair about 0.4 millimeter apart. The distance is so small that the two points may, for all ordinary constructions, be regarded as coincident.

[2] The optical power of a lens is the reciprocal of its focal length. The dioptry or unit of optical power is the power of a lens with a focal length of 1 meter.

points of the object through the above-mentioned nodal point and to prolong them till they strike the retina. It is evident that the size of the retinal image will be as much smaller than that of the object as the distance of the nodal point from the retina is smaller than its distance from the object.

According to the figures above given, the nodal point is about 7.2 millimeters behind the anterior surface of the cornea and about 15.0 millimeters in front of the retina. Hence the size of the retinal image of an object of known size and distance can be readily calculated—a problem which has frequently to be solved in the study of physiological optics. The construction given in Figure 216 shows that from all external objects *inverted* images are projected upon the retina, and such inverted images can actually be seen under favorable conditions. If, for instance, the eye of a white rabbit, which contains no choroidal pigment, be excised and held with the cornea directed toward a window or other source of light, an inverted image of the luminous object will be seen through the transparent sclerotic in the same way that one sees an inverted image of a landscape on the ground-glass plate of a photographic camera. The question is often asked, " Why, if the images are inverted in the retina, do we not see objects upside down?" The only answer to such a question is that it is precisely *because* images are inverted on the retina that we do *not* see objects upside down, for the eye has learned through lifelong practice to associate an impression made upon any portion of the retina with light coming from the *opposite* portion of the field of vision. Thus if an image falls upon the lower portion of the retina, our experience, gained chiefly through muscular movements and tactile sensations, has taught us that this image must correspond to an object in the upper portion of our field of vision. In whatever way the retina is stimulated the same effect is produced. If, for instance, gentle pressure is made with the finger on the lateral portion of the eyeball through the closed lids a circle of light known as a phosphene immediately appears on the opposite side of the eye. Another good illustration of the same general rule is found in the effect of throwing a shadow upon the retina from an object as close as possible to the eye. For this purpose place a card
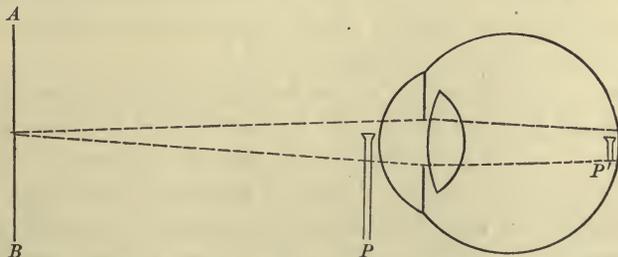
Fig. 217.—Diagram illustrating the projection of a shadow on the retina.

with a small pin-hole in it in front of a source of light, and three or four centimeters distant from the eye. Then hold some object smaller than the pupil—*e. g.* the head of a pin—as close as possible to the cornea. Under these conditions neither the pin-hole nor the pin-head can be really seen—*i. e.* they

are both too near to have their image focussed upon the retina. The pin-hole becomes itself a source of light, and appears as a luminous circle bounded by the shadow thrown by the edge of the iris. Within this circle of light is seen the shadow of the pin-head, but the pin-head appears *inverted*, for the obvious reason that the eye, being accustomed to interpret all retinal impressions as corresponding to objects in the opposite portion of the field of vision, regards the upright shadow of the pin-head as the representation of an inverted object. The course of the rays in this experiment is shown in Figure 217, in which *A B* represents the card with a pin-hole in it, *P* the pin, and *P'* its upright shadow thrown on the retina.

Accommodation.—From what has been said of conjugate foci and their relation to each other it is evident that any change in the distance of the object from the refracting media will involve a corresponding change in the position of the image, or, in other words, only objects at a given distance can be focussed upon a plane which has a fixed position with regard to the refracting surface or surfaces. Hence all optical instruments in which the principle of conjugate foci finds its application have adjustments for distance. In the telescope and opera-glass the adjustment is effected by changes in the distance between the lenses, and in the photographic camera by a change in the position of the ground-glass plate representing the focal plane. In the microscope the adjustment is effected by changing the distance of the object to suit the lenses, the higher powers having a shorter " working distance."

We must now consider in what way the eye adapts itself to see objects distinctly at different distances. That this power of adaptation, or "accommodation," really exists we can easily convince ourselves by looking at different objects through a network of fine wire held near the eyes. When with normal vision the eyes are directed to the distant objects the network nearly disappears, and if we attempt to see the network distinctly the outlines of the distant objects become obscure. In other words, it is impossible to see both the network and the distant objects distinctly at the same time. It is also evident that in accommodation for distant objects the eyes are at rest, for when they are suddenly opened after having been closed for a short time they are found to be accommodated for distant objects, and we are conscious of a distinct effort in directing them to any near object.[1]

From the optical principles above described it is clear that the accommodation of the eye for near objects may be conceived of as taking place in three different ways: 1st, By an increase of the distance between the refracting surfaces of the eye and the retina; 2d, By an increase of the index of refraction of one or more of the media; 3d, By a diminution of the radius of curvature of one or more of the surfaces. The first of these methods was formerly supposed to be the one actually in use, a lengthening of the eyeball under a pres-

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[1] It has been shown by Beer (*Archiv für die gesammte Physiologie*, lviii. 523) that in fishes the eyes when at rest are accommodated for *near* objects, and that accommodation for *distant* objects is effected by the contraction of a muscle for which the name "retractor lentis" is proposed.

sure produced by the eye-muscles being assumed to occur. This lengthening would, in the case of a normal eye accommodating itself for an object at a distance of 15 centimeters, amount to not less than 2 millimeters—a change which could hardly be brought about by the action of any muscles connected with the eye. Moreover, accommodation changes can be observed upon electrical stimulation of the excised eye. Its mechanism must, therefore, lie within the eye itself. As for the second of these methods, there is no conceivable way by which a change in the index of refraction of the media can be effected, and we are thus forced to the conclusion that accommodation is brought about by a change in the curvature of the refracting surfaces—*i. e.* by a method quite different from any which is employed in optical instruments of human construction. Now, by measuring the curvature of the cornea of a person who looks alternately at near and distant objects it has been shown that the cornea undergoes no change of form in the act of accommodation. By a process of exclusion, therefore, the lens is indicated as the essential organ in this function of the eye, and, in fact, the complicated structure and connections of the lens at once suggest the thought that it is in the surfaces of this portion of the eye that the necessary changes take place. Indeed, from a teleological point of view the lens would seem somewhat superfluous if it were not important to have a transparent refracting body of *variable* form in the eye, for the amount of refraction which takes place in the lens could be produced by a slightly increased curvature of the cornea. Now, the changes of curvature which occur in the surfaces of the lens when the eye is directed to distant and near objects alternately can be actually observed and measured with considerable accuracy. For this purpose the changes in the form, size, and position of the images of brilliant objects reflected in these two surfaces are studied. If a candle is held in a dark room on a level with and about 50 centimeters away from the eye in which the accommodation is to be studied, an observer, so placed that his own axis of vision makes about the same angle (15°–20°) with that of the observed eye that is made by a line joining the observed eye and the candle, will readily see a small upright image of the candle reflected in the cornea of the observed eye. Near this and within the outline of the pupil are two other images of the candle, which, though much less easily seen than the corneal image, can usually be made out by a proper adjustment of the light. The first of these is a large faint upright image reflected from the anterior surface of the lens, and the second is a small inverted image reflected from the posterior surface of the lens. It will be observed that the size of these images varies with the radius of curvature of the three reflecting surfaces as given on p. 749. The relative size and position of these images having been recognized while the eye is at rest—*i. e.* is accommodated for distance—let the person who is under observation be now requested to direct his eye to a near object lying in the same direction. When this is done the corneal image and that reflected from the posterior surface of the lens will remain unchanged,[1]

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[1] A very slight diminution in size may sometimes be observed in the image reflected from the posterior surface of the lens.

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while that reflected from the anterior surface of the lens will become smaller and move toward the corneal image. This change in the size and position of the reflected image can only mean that the surface from which the reflection takes place has become more convex and has moved forward. Coincident with this change a contraction of the pupil will be observed.

An apparatus for making observations of this sort is known as the phakoscope of Helmholtz (Fig. 218). The eye in which the changes due to accommodation are to be observed is placed at an opening in the back of the instrument at *C*, and directed alternately to a needle placed in the opening *D* and to a distant object lying in the same direction. Two prisms at *B* and *B'* serve to throw the light of a candle on to the observed eye, and the eye of an observer at *A* sees the three reflected images, each as two small square spots of light. The movement and the change of size of the image reflected from the anterior surface of the lens can be thus much better observed than when a candle-flame is used.

FIG. 218.—Phakoscope of Helmholtz.

The course of the rays of light in this experiment is shown diagrammatically in Figure 219. The observed eye is directed to the point *A*, while the candle and the eye of the observer are placed symmetrically on either side. The images of the candle reflected from the various surfaces of the eye will be seen projected on the dark background of the pupil
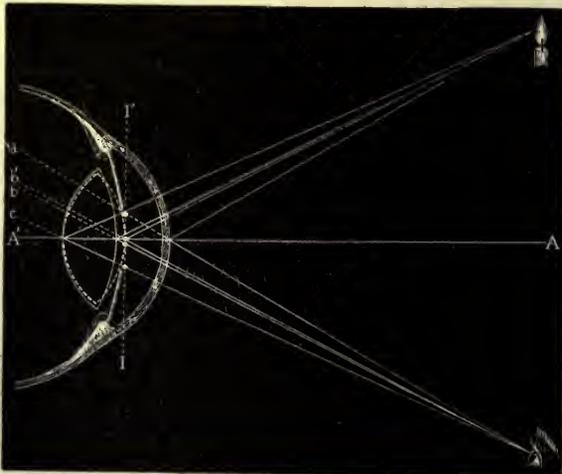
FIG. 219.—Diagram explaining the change in the position of the image reflected from the anterior surface of the crystalline lens (Williams, after Donders).

in the directions indicated by the dotted lines ending at *a*, *b*, and *c*. When the eye is accommodated for a near object the middle one of the three images moves nearer the corneal image—*i. e.* it changes in its direction from *b* to *b'*, showing that the anterior surface of the lens has bulged forward into the position indi-

cated by the dotted line. The change in the appearance of the images is
represented diagrammatically in Figure 220. On the left is shown the appear-
ance of the images as seen when the eye is at rest, *a* representing the corneal
image, *b* that reflected from the anterior, and *c* that from the posterior surface
of the lens when the observing eye and the candle are in the position repre-
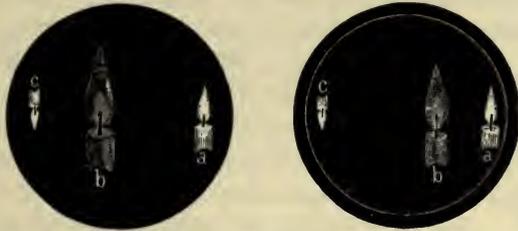
Fig. 220.—Reflected images of a candle-flame as seen in the pupil of an eye at rest and accommodated
for near objects (Williams).

sented in Figure 219. The images are represented as they appear in the dark
background of the pupil, though of course the corneal image may, in certain
positions of the light, appear outside of the pupillary region. When the eye
is accommodated for near objects the images appear as shown in the circle on
the right, the image *b* becoming smaller and brighter and moving toward the
corneal image, while the pupil contracts as indicated by the circle drawn round
the images.

The changes produced in the eye by an effort of accommodation are indi-
cated in Figure 221, the left-hand side of the diagram showing the condition
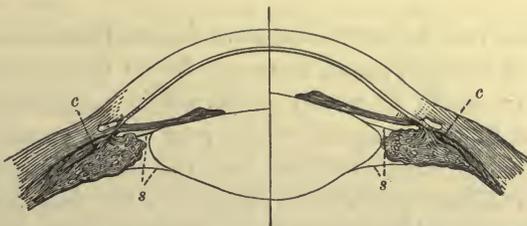
Fig. 221.—Showing changes in the eye produced by the act of accommodation (Helmholtz).

of the eye at rest, and the right-hand side that in extreme accommodation for
near objects.

It will be observed that the iris is pushed forward by the bulging lens and
that its free border approaches the median line. In other words, the pupil is
contracted in accommodation for near objects. The following explanation of
the mechanism by which this change in the shape of the lens is effected has
been proposed by Helmholtz, and is still generally accepted. The structure
of the lens is such that by its own elasticity it tends constantly to assume a
more convex form than the pressure of the capsule and the tension of the sus-
pensory ligaments (*s, s*, Fig. 221) allow. This pressure and tension are dimin-
ished when the eye is accommodated for near vision by the contraction of the
ciliary muscles (*c, c*, Fig. 221), most of whose fibres, having their origin at the

point of union of the cornea and sclerotic, extend radially outward in every direction and are attached to the front part of the choroid. The contraction of the ciliary muscle, drawing forward the membranes of the eye, will relax the tension of the suspensory ligament and allow the lens to take the form determined by its own elastic structure. According to another theory of accommodation proposed by Tscherning,[1] the suspensory ligament is stretched and not relaxed by the contraction of the ciliary muscle.

In consequence of the pressure thus produced upon the lens, the soft external portions are moulded upon the harder nuclear portion in such a way as to give to the anterior (and to some extent to the posterior) surface a hyperboloid instead of a spherical form. A similar theory has been recently brought forward by Schoen,[2] who compares the action of the ciliary muscle upon the lens to that of the fingers compressing a rubber ball, as shown in Figure 222. These theories have an advantage over that offered by Helmholtz, inasmuch as they afford an explanation of the presence in the ciliary muscle of circular fibres, which, on the theory of Helmholtz, seem to be superfluous. They also make the fact of so-called "astigmatic accommodation" comprehensible. This term is applied to the power said to be sometimes gradually acquired by persons with astigmatic[3] eyes of correcting this defect of vision by accommodating the eye more strongly in one meridian than another.[4]

FIG. 222.—To illustrate Schoen's theory of accommodation.

Whatever views may be entertained as to the exact mechanism by which its change of shape is brought about, there can be no doubt that the lens is the portion of the eye chiefly or wholly concerned in accommodation, and it is accordingly found that the removal of the lens in the operation for cataract destroys the power of accommodation, and the patient is compelled to use convex lenses for distant and still stronger ones for near objects.

It is interesting to notice that the act of accommodation, though distinctly voluntary, is performed by the agency of the *unstriped* fibres of the ciliary muscles. It is evident, therefore, that the term "involuntary" sometimes applied to muscular fibres of this sort may be misleading. The voluntary character of the act of accommodation is not affected by the circumstance that the will needs, as a rule, to be assisted by visual sensations. The fact that most persons cannot affect the necessary change in the eye unless they direct their attention to some near or far object is only an instance of the close relation between sensory impressions and motor impulses, which is further exem-

[1] *Archives de Physiologie*, 1894, p. 40. [2] *Archiv für die gesammte Phys.*, lix. 427.
[3] See p. 763.
[4] Recent observations by Hess (*Archiv f. Ophthalmologie*, xlii. 288) tend to confirm the Helmholtz theory by showing that the suspensory ligament is relaxed and not stretched in accommodation for near objects.

plified by such phenomena as the paralysis of the lip of a horse caused by the division of the trifacial nerve. It is found, moreover, that by practice the power of accommodating the eye without directing it to near and distant objects can be acquired. The nerve-channels through which accommodation is affected are the anterior part of the nucleus of the third pair of nerves lying in the extreme hind part of the floor of the third ventricle, the most anterior bundle of the nerve-root, the third nerve itself, the lenticular ganglion, and the short ciliary nerves (see diagram p. 769).

The mechanism of accommodation is affected in a remarkable way by drugs, the most important of which are atropia and physostigmin, the former paralyzing and the latter stimulating the ciliary muscle. As these drugs exert a corresponding effect upon the iris, it will be convenient to discuss their action in connection with the physiology of that organ.

The changes occurring in the eye during the act of accommodation are indicated in the following table, which shows, both for the actual and the reduced eye, the extent to which the refracting media change their form and position, and the consequent changes in the position of the foci :

		Accommodation for	
Actual Eye.	distant objects.	near objects.	
Radius of cornea	8	mm.	8	mm.
Radius of anterior surface of lens	10	"	6	"
Radius of posterior surface of lens	6	"	5.5	"
Distance from cornea to anterior surface of lens . .	3.6	"	3.2	"
Distance from cornea to posterior surface of lens . .	7.2	"	7.2	"
Reduced Eye.			
Radius of curvature	5.02	"	4.48	"
Distance from cornea to principal point	2.15	"	2.26	"
Distance from cornea to nodal point	7.16	"	6.74	"
Distance from cornea to anterior focus	12.918	"	11.241	"
Distance from cornea to posterior focus	22.231	"	20.248	"

It will be noticed that no change occurs in the curvature of the cornea, and next to none in the posterior surface of the lens, while the anterior surface of the lens undergoes material alterations both in its shape and position.

Associated with the accommodative movements above described, two other changes take place in the eyes to adapt them for near vision. In the first place, the axes of the eyes are converged upon the near object, so that the images formed in the two eyes shall fall upon corresponding points of the retinas, as will be more fully explained in connection with the subject of binocular vision. In the second place, the pupil becomes contracted, thus reducing the size of the pencil of rays that enters the eye. The importance of this movement of the pupil will be better understood after the subject of spherical aberration of light has been explained. These three adjustments, focal, axial, and pupillary, are so habitually associated in looking at near objects that the axial can only by an effort be dissociated from the other two, while these two are quite inseparable from one another. This may be illustrated by a simple experiment. On a sheet of paper about 40 centimeters distant

from the eyes draw two letters or figures precisely alike and about 3 centimeters apart. (Two letters cut from a newspaper and fastened to the sheet will answer the same purpose.) Hold a small object like the head of a pin between the eyes and the paper at the point of intersection of a line joining the right eye and the left letter with a line joining the left eye and the right letter. If the axes of vision are converged upon the pin-head, that object will be seen distinctly, and beyond it will be seen indistinctly *three* images of the letter, the central one being formed by the blending of the inner one of each pair of images formed on the two retinas. If now the attention be directed to the middle image, it will gradually become perfectly distinct as the eye accommodates itself for that distance. We have thus an axial adjustment for a very near object and a focal adjustment for a more distant one. If the pupil of the individual making this observation be watched by another person, it will be found that at the moment when the middle image of the letter becomes distinct the pupil, which had been contracted in viewing the pin-head, suddenly dilates. It is thus seen that when the axial and focal adjustments are dissociated from each other the pupillary adjustment allies itself with the latter.

The opposite form of dissociation—viz. the axial adjustment for distance and the focal adjustment for near vision—is less easy to bring about. It may perhaps be best accomplished by holding a pair of stereoscopic pictures before the eyes and endeavoring to direct the right eye to the right and the left eye to the left picture—*i. e.* to keep the axes of vision parallel while the eyes are accommodated for near objects. One who is successful in this species of ocular gymnastics sees the two pictures blend into one having all the appearance of a solid object. The power of thus studying stereoscopic pictures without a stereoscope is often a great convenience to the possessor, but individuals differ very much in their ability to acquire it.

Range of Accommodation.—By means of the mechanism above described it is possible for the eye to produce a distinct image upon the retina of objects lying at various distances from the cornea. The point farthest from the eye at which an object can be distinctly seen is called the *far-point*, and the nearest point of distinct vision is called the *near-point* of the eye, and the distance between the near-point and the far-point is called the range of distinct vision or the *range of accommodation*. As the normal emmetropic eye is adapted, when at rest, to bring parallel rays of light to a focus upon the retina, its far-point may be regarded as at an infinite distance. Its near-point varies with age, as will be described under Presbyopia. In early adult life it is from 10 to 13 centimeters from the eye. For every point within this range there will be theoretically a corresponding condition of the lens adapted to bring rays proceeding from that point to a focus on the retina, but as rays reaching the eye from a point 175 to 200 centimeters distant do not, owing to the small size of the pupil, differ sensibly from parallel rays, there is no appreciable change in the lens unless the object looked at lies within that distance. It is also evident that as an object approaches the eye a given change of distance will cause a constantly increasing amount of divergence of the rays proceeding from

it, and will therefore necessitate a constantly increasing amount of change in the lens to enable it to focus the rays on the retina. We find, accordingly, that all objects more than two meters distant from the eye can be seen distinctly at the same time—*i. e.* without any change in the accommodative mechanism— but for objects within that distance we are conscious of a special effort of accommodation which becomes more and more distinct the shorter the distance between the eye and the object.

Myopia and Hypermetropia.—There are two conditions of the eye in which the range of accommodation may differ from that which has just been described as normal. These conditions, which are too frequent to be regarded (except in extreme cases) as pathological, are generally dependent upon the eyeball being unduly lengthened or shortened. In Fig. 223 are shown diagrammatically the three conditions known as emmetropia, myopia, and hypermetropia. In the normal or emmetropic eye, *A*, parallel rays are represented as brought to a focus on the retina; in the short-sighted, or myopic, eye, *B*, similar rays are focussed in front of the retina, since the latter is abnormally distant; while in the over-sighted, or hypermetropic, eye, *C*, they are focussed behind the retina, since it is abnormally near.

It is evident that when the eye is at rest both the myopic and the hypermetropic eye will see distant objects indistinctly, but there is this important difference: that in hypermetropia the difficulty can be corrected by an effort of accommodation, while in myopia this is impossible, since there is no mechanism by which

Fig. 223.—Diagram showing the difference between normal, myopic, and hypermetropic eyes.

the radius of the lenticular surfaces can be increased. Hence an individual affected with myopia is always aware of the infirmity, while a person with hypermetropic eyes often goes through life unconscious of the defect. In this case the accomodation is constantly called into play even for distant objects, and if the hypermetropia is excessive, any prolonged use of the eyes is apt to be attended by a feeling of fatigue, headache, and a train of nervous symptoms familiar to the ophthalmic surgeon. Hence it is important to discover this defect where it exists and to apply the appropriate remedy—viz. convex lenses placed in front of the eyes in order to make the rays slightly convergent when they enter the eye. Thus aided, the refractive power of the eye at rest is sufficient to bring the rays to a focus upon the retina and thus relieve the accommoda-

tion. This action of a convex lens in hypermetropia is indicated by the dotted lines in Fig. 222, *C*, and the corresponding use of a concave lens in myopia is shown in Fig. 222, *B*.

The detection and quantitative determination of hypermetropia are best made after the accommodation has been paralyzed by the use of atropia, by ascertaining how strong a convex lens must be placed before the eye to produce distinct vision of distant objects.

The range of accommodation varies very much from the normal in myopic and hypermetropic eyes. In myopia the near-point is often 5 or 6 centimeters from the cornea, while the far-point, instead of being infinitely far off, is at a variable but no very great distance from the eye. The range of accommodation is therefore very limited. In hypermetropia the near-point is slightly farther than normal from the eye, and the far-point cannot be said to exist, for the eye at rest is adapted to bring converging rays to a focus on the retina, and such pencils of rays do not exist in nature. Mathematically, the far-point may be said to be at more than an infinite distance from the eye. The range of effective accommodation is therefore reduced, for a portion of the accommodative power is used up in adapting the eye to receive parallel rays.

Presbyopia.—The power of accommodation diminishes with age, owing apparently to a loss of elasticity of the lens. The change is regularly progressive, and can be detected as early as the fifteenth year, though in normal eyes it does not usually attract attention until the individual is between forty and forty-five years of age. At this period of life a difficulty is commonly experienced in reading ordinary type held at a convenient distance from the eye, and the individual becomes old-sighted or *presbyopic*—a condition which can, of course, be remedied by the use of convex glasses. Cases are occasionally reported of persons recovering their power of near vision in extreme old age and discontinuing the use of the glasses previously employed for reading. In these cases there is apparently not a restoration of the power of accommodation, but an increase in the refractive power of the lens through local changes in its tissue. A diminution in the size of the pupil, sometimes noticed in old age, may also contribute to the distinctness of the retinal image, as will be described in connection with spherical aberration.

Defects of the Dioptric Apparatus.—The above-described imperfections of the eye—viz. myopia and hypermetropia—being generally (though not invariably) due to an abnormal length of the longitudinal axis, are to be regarded as defects of construction affecting only a comparatively small number of eyes. There are, however, a number of imperfections of the dioptric apparatus, many of which affect all eyes alike. Of these imperfections some affect the eye in common with all optical instruments, while others are peculiar to the eye and are not found in instruments of human construction. The former class will be first considered.

Spherical Aberration.—It has been stated that a pencil of rays falling upon a spherical refracting surface will be refracted to a common focus. Strictly speaking, however, the outer rays of the pencil—*i. e.* those which fall

near the periphery of the refracting surface—will be refracted more than those which lie near the axis and will come to a focus sooner. This phenomenon, which is called spherical aberration, is more marked with diverging than with parallel rays, and tends, of course, to produce an indistinctness of the image which will increase with the extent of the surface through which the rays pass. The effect of a diaphragm used in many optical instruments to reduce the amount of spherical aberration by cutting off the side rays is shown diagrammatically in Fig. 224.
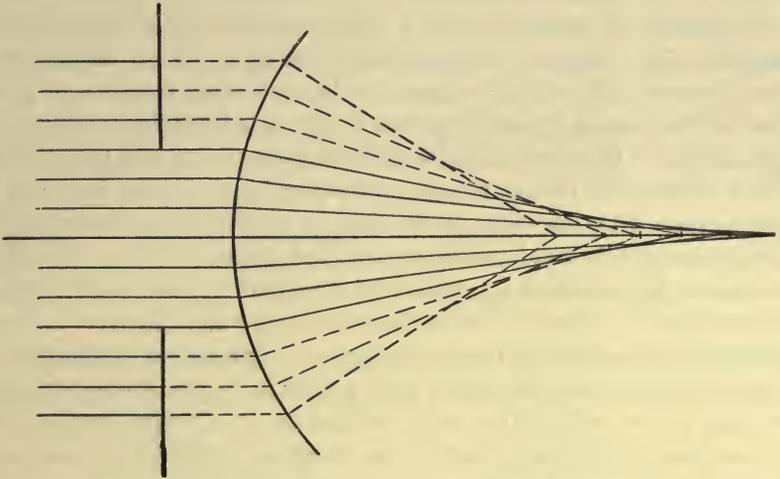
Fig. 224.—Diagram showing the effect of a diaphragm in reducing the amount of spherical aberration.

The rôle of the iris in the vision of near objects is now evident, for when the eye is directed to a near object the spherical aberration is increased in consequence of the rays becoming more divergent, but the contraction of the pupil which accompanies accommodation tends, by cutting off the side rays, to prevent a blurring of the image which otherwise would be produced. It must, however, be remembered that the crystalline lens, unlike any lens of human construction, has a greater index of refraction at the centre than at the periphery. This, of course, tends to correct spherical aberration, and, in so far as it does so, to render the cutting off of the side rays unnecessary. Indeed, the total amount of possible spherical aberration in the eye is so small that its effect on vision may be regarded as insignificant in comparison with that caused by the other optical imperfections of the eye.

Chromatic Aberration.—In the above account of the dioptric apparatus of the eye the phenomena have been described as they would occur with monochromatic light—*i. e.* with light having but one degree of refrangibility. But the light of the sun is composed of an infinite number of rays of different degrees of refrangibility. Hence when an image is formed by a simple lens the more refrangible rays—*i. e.* the violet rays of the spectrum—are brought to a focus sooner than the less refrangible red rays. The image therefore

appears bordered by fringes of colored light. This phenomenon of *chromatic aberration* can be well observed by looking at objects through the lateral portion of a simple lens, or, still better, by observing them through two simple lenses held at a distance apart equal to the sum of their focal distances. The objects will appear inverted (as through an astronomical telescope) and surrounded with borders of colored light. Now, the chromatic aberration of the eye is so slight that it is not easily detected, and the physicists of the eighteenth century, in their efforts to produce an achromatic lens, seem to have been impressed by the fact that in the eye a combination of media of different refractive powers is employed, and to have sought in this circumstance an explanation of the supposed achromatism of the eye. Work directed on this line was crowned with brilliant success, for by combining two sorts of glass of different refractive and dispersive powers it was found possible to refract a ray of light without dispersing it into its different colored rays, and the achromatic lens, thus constructed, became at once an essential part of every first-class optical instrument. Now, as there is not only no evidence that the principle of the achromatic lens is employed in the eye, but distinct evidence that the eye is uncorrected for chromatic aberration, we have here a remarkable instance of a misconception of a physical fact leading to an important discovery in physics. The chromatic aberration of the eye, though so slight as not to interfere at all with ordinary vision, can be readily shown to exist by the simple experiment of covering up one half of the pupil and looking at a bright source of light e. g. a window. If the lower half of the pupil be covered, the cross-bars of
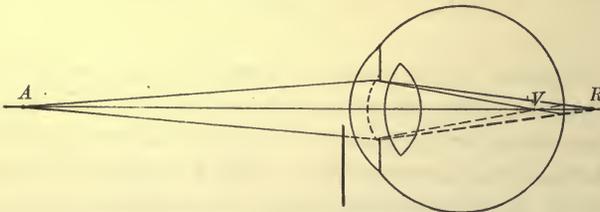
Fig. 225.—Diagram to illustrate chromatic aberration.

the window will appear bordered with a fringe of blue light on the lower and reddish light on the upper side. The explanation usually given of the way in which this result is produced is illustrated in Fig. 225. Owing to the chromatic aberration of the eye all the rays emanating from an object at A are not focussed accurately on the retina, but if the eye is accommodated for a ray of medium refrangibility, the violet rays will be brought to a focus in front of the retina at V, while the red rays will be focussed behind the retina at R. On the retina itself will be formed not an accurate optical image of the point A, but a small circle of dispersion in which the various colored rays are mixed together, the violet rays after crossing falling upon the same part of the retina as the red rays before crossing. Thus by a sort of compensation, which, however, cannot be equivalent to the synthetic reproduction of white light by the union of the spectral colors, the disturbing effect of chromatic aberration is

diminished. When the lower half of the pupil is covered by the edge of a card held in front of the cornea at D, the aberration produced in the upper half of the eye is not compensated by that of the lower half. Hence the image of a point of white light at A will appear as a row of spectral colors on the retina, and all objects will appear bordered by colored fringes. Another good illustration of the chromatic aberration of the eye is obtained by cutting two holes of any convenient shape in a piece of black cardboard and placing behind one of them a piece of blue and behind the other a piece of red glass. If the card is placed in a window some distance (10 meters) from the observer, in such a position that the white light of the sky may be seen through the colored glasses, it will be found that the outlines of the two holes will generally be seen with unequal distinctness. To most eyes the red outline will appear quite distinct, while the blue figure will seem much blurred. To a few individuals the blue figure appears the more distinct, and these will generally be found to be hypermetropic.

Astigmatism.—The defect known as astigmatism is due to irregularities of curvature of the refracting surfaces, in consequence of which all the rays proceeding from a single point cannot be brought to a single focus on the retina.

Astigmatism is said to be *regular* when one of the surfaces, generally the cornea, is not spherical, but ellipsoidal—*i. e.* having meridians of maximum
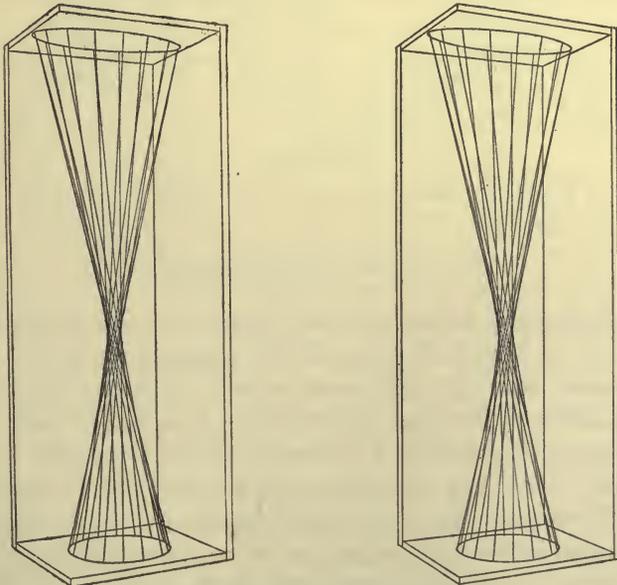
FIG. 226.—Model to illustrate astigmatism.

and minimum curvature at right angles to each other, though in each meridian the curvature is regular. When this is the case the rays proceeding from a single luminous point are brought to a focus earliest when they lie in the meridian in which the surface is most convex. Hence the pencil of rays will

have two linear foci, at right angles to the meridians of greatest and least curvature separated by a space in which a section of the cone of rays will be first elliptical, then circular, and then again elliptical. This defect exists to a certain extent in nearly all eyes, and is, in some cases, a serious obstacle to distinct vision. The course of the rays when thus refracted is illustrated in Fig. 226, which represents the interior of a box through which black threads are drawn to indicate the course of the rays of light. The threads start at one end of the box from a circle representing the cornea, and converge with different degrees of rapidity in different meridians, so that a section of the cone of rays will be successively an ellipse, a straight line, an ellipse, a circle, etc., as shown by the model represented in Fig. 227. It will be noticed that this and the preced-
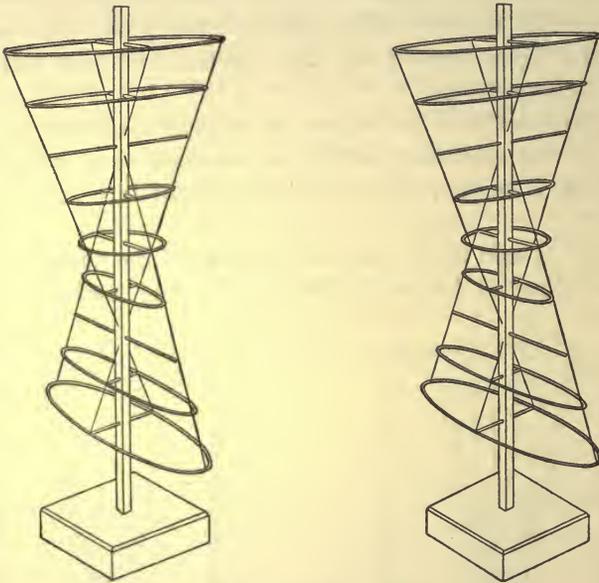
Fig. 227.—Model to illustrate astigmatism.

ing figure are drawn in duplicate, but that the lines are not precisely alike on the two sides. In fact, the lines on the left represent the model as it would be seen with the right eye, and those on the right as it would appear to the left eye, which is just the opposite from an ordinary stereoscopic slide. The figures are drawn in this way because they are intended to produce a "pseudoscopic" effect in a way which will be explained in connection with the subject of binocular vision. For this purpose it is only necessary to cross the axes of vision in front of the page, as in the experiment described on page 758, for studying the relation between the focal, axial, and pupillary adjustments of the eye. As soon as the middle image becomes distinct it assumes a stereoscopic appearance, and the correct relations between the different parts of the model are at once obvious.

This imperfection of the eye may be detected by looking at lines such as are shown in Figure 228, and testing each eye separately. If the straight lines

drawn in various directions through a common point cannot be seen with equal distinctness at the same time, it is evident that the eye is better adapted to focus rays in one meridian than in another—*i. e.* it is astigmatic. The concentric
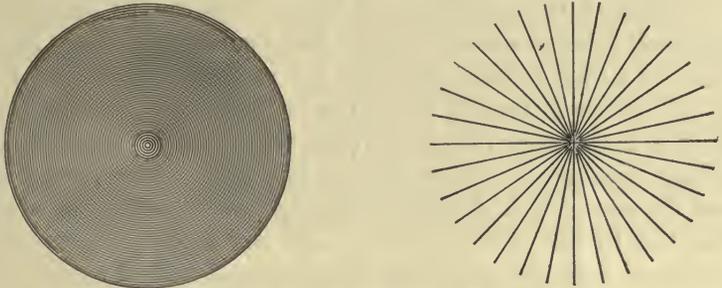
Fig. 228.—Lines for the detection of astigmatism.

circles are a still more delicate test. Few persons can look at this figure attentively without noticing that the lines are not everywhere equally distinct, but that in certain sectors the circles present a blurred appearance. Not infrequently it will be found that the blurred sectors do not occupy a constant position, but oscillate rapidly from one part of the series of circles to another. This phenomenon seems to be due to slight involuntary contractions of the ciliary muscle causing changes in accommodation.

The direction of the meridians of greatest and least curvature of the cornea of a regularly astigmatic eye, and the difference in the amount of this curvature, can be very accurately measured by means of the ophthalmometer (see p. 750). These points being determined, the defect of the eye can be perfectly corrected by cylindrical glasses adapted to compensate for the excessive or deficient refraction of the eye in certain meridians.

By another method known as "skiascopy," which consists in studying the light reflected from the fundus of the eye when the ophthalmoscopic mirror is moved in various directions, the amount and direction of the astigmatism of the eye as a whole (and not that of the cornea alone) may be ascertained.

Astigmatism is said to be irregular when in certain meridians the curvatures of the refracting surfaces are not arcs of circles or ellipses, or when there is a lack of homogeneousness in the refracting media. This imperfection exists to a greater or less extent in all eyes, and, unlike regular astigmatism, is incapable of correction. It manifests itself by causing the outlines of all brilliant objects to appear irregular. It is on this account that the fixed stars do not appear to us like points of light, but as luminous bodies with irregular "star"-shaped outlines. The phenomenon can be conveniently studied by looking at a pinhole in a large black card held at a convenient distance between the eye and a strong light. The hole will appear to have an irregular outline, and to some eyes will appear double or treble.

Intraocular Images.—Light entering the eye makes visible, under certain circumstances, a number of objects which lie within the eye itself. These objects are usually opacities in the media of the eye which are ordinarily invisi-

ble, because the retina is illuminated by light coming from all parts of the pupil, and with such a broad source of light no object, unless it is a very large one or one lying very near the back of the eye, can cast a shadow on the retina. Such shadows can, however, be made apparent by allowing the media of the eye to be traversed by parallel rays of light. This can be accomplished by holding a small polished sphere—*e. g.* the steel head of a shawl-pin illuminated by sunlight or strong artificial light—in the anterior focus of the eye—*i. e.* about 22 millimeters in front of the cornea, or by placing a dark screen with a pin-hole in it in the same position between the eye and a source of uniform diffused light, such as the sky or the porcelain shade of a student lamp. In either case the rays of light diverging from the minute source will be refracted into parallelism by the media of the eye, and will produce the sensation of a circle of diffused light, the size of which will depend upon the amount of dilatation of the pupil. Within this circle of light will be seen the shadows of any opaque substances that may be present in the media of the eye. These shadows, being cast by parallel rays, will be of the same size as the objects themselves, as is shown diagrammatically in Figure 229, in which *A* represents a source
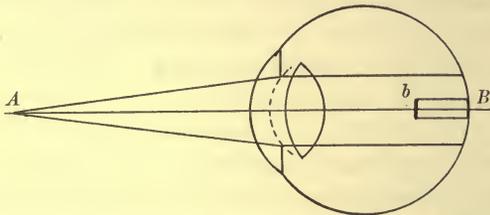
FIG. 229.—Showing the method of studying intraocular images (Helmholtz).

of light at the anterior focus of the eye, and *b* an opacity in the vitreous humor casting a shadow *B* of the same size as itself upon the retina. It is evident that if the source of light *A* is moved from side to side the various opacities will be displaced relatively to the circle of light surrounding them by an amount depending upon the distance of the opacities from the retina. A study of these displacements will therefore afford a means of determining the position of the opacities within the media of the eye.

Muscæ Volitantes.—Among the objects to be seen in thus examining the eye the most conspicuous are those known as the *muscæ volitantes.* These present themselves in the form of beads, either singly or in groups, or of streaks, patches, and granules. They have an almost constant floating motion, which is increased by the movements of the eye and head. They usually avoid the line of vision, floating away when an attempt is made to fix the sight upon them. When the eye is directed vertically, however, they sometimes place themselves directly in line with the object looked at. If the intraocular object is at the same time sufficiently near the back of the eye to cast a shadow which is visible without the use of the focal illumination, some inconvenience may thus be caused in using a vertical microscope.

A study of the motions of the *muscæ volitantes* makes it evident that the

phenomenon is due to small bodies floating in a liquid medium of a little greater specific gravity than themselves. Their movements are chiefly in planes perpendicular to the axis of vision, for when the eye is directed vertically upward they move as usual through the field of vision without increasing the distance from the retina. They are generally supposed to be the remains of the embyronic structure of the vitreous body—*i. e.* portions of the cells and fibres which have not undergone complete mucous transformation.

In addition to these floating opacities in the vitreous body various other defects in the transparent media of the eye may be revealed by the method of focal illumination. Among these may be mentioned spots and stripes due to irregularities in the lens or its capsule, and radiating lines indicating the stellate structure of the lens.

Retinal Vessels.—Owing to the fact that the blood-vessels ramify near the anterior surface of the retina, while those structures which are sensitive to light constitute the posterior layer of that organ, it is evident that light entering the eye will cast a shadow of the vessels on the light-perceiving elements of the retina. Since, however, the diameter of the largest blood-vessels is not more than one-sixth of the thickness of the retina, and the diameter of the pupil is one-fourth or one-fifth of the distance from the iris to the retina, it is evident that when the eye is directed to the sky or other broad illuminated surfaces it is only the *penumbra* of the vessels that will reach the rods and cones, the *umbra* terminating conically somewhere in the thickness of the retina. But if light is allowed to enter the eye through a pin-hole in a card held a short distance from the cornea, as in the above-described method of focal illumination, a sharply defined shadow of the vessels will be thrown on the rods and cones. Yet under these conditions the retinal vessels are not rendered visible unless the perforated card is moved rapidly to and fro, so as to throw the shadow continually on to fresh portions of the retinal surface. When this is done the vessels appear, ramifying usually as dark lines on a lighter background, but the dark lines are sometimes bordered by bright edges. It will be observed that those vessels appear most distinctly the course of which is at right angles to the direction in which the card is moved. Hence in order to see all the vessels with equal distinctness it is best to move the card rapidly in a circle the diameter of which should not exceed that of the pupil. In this manner the distribution of the vessels in one's own retina may be accurately observed, and in many cases the position of the fovea centralis may be determined by the absence of vessels from that portion of the macula lutea.

The retinal vessels may also be made visible in several other ways—*e. g.*, 1. By directing the eye toward a dark background and moving a candle to and fro in front of the eye, but below or to one side of the line of vision. 2. By concentrating a strong light by means of a lens of short focus upon a point of the sclerotic as distant as possible from the cornea. By either of these methods a small image of the external source of light is formed upon the lateral portion of the eye, and this image is the source of light which throws shadows of the retinal vessels on to the rods and cones.

Circulation of Blood in the Retina.—When the eye is directed toward a surface which is uniformly and brightly illuminated—*e. g.* the sky or a sheet of white paper on which the sun is shining—the field of vision is soon seen to be filled with small bright bodies moving with considerable rapidity in irregular curved lines, but with a certain uniformity which suggests that their movements are confined to definite channels. They are usually better seen when one or more sheets of cobalt glass are held before the face, so that the eyes are bathed in blue light. That the phenomenon depends upon the circulation of the blood globules in the retina is evident from the fact that the moving bodies follow paths which correspond with the form of the retinal capillaries as seen by the methods above described, and also from the correspondence between the rate of movement of the intraocular image and the rapidity of the capillary circulation in those organs in which it can be directly measured under the microscope. The exact way in which the moving globules stimulate the retina so as to produce the observed phenomenon must be regarded as an unsettled question.

We have thus seen that the eye, regarded from the optician's point of view, has not only all the faults inherent in optical instruments generally, but many others which would not be tolerated in an instrument of human construction. Yet with all its imperfections the eye is perhaps the most wonderful instance in nature of the development of a highly specialized organ to fulfil a definite purpose. In the accomplishment of this object the various parts of the eye have been perfected to a degree sufficient to enable it to meet the requirements of the nervous system with which it is connected, and no farther. In the ordinary use of the eye we are unconscious of its various irregularities, shadows, opacities, etc., for these imperfections are all so slight that the resulting inaccuracy of the image does not much exceed the limit which the size of the light-perceiving elements of the retina imposes upon the delicacy of our visual perceptions, and it is only by illuminating the eye in some unusual way that the existence of these imperfections can be detected. In other words, the eye is as good an optical instrument as the nervous system can appreciate and make use of. Moreover, when we reflect upon the difficulty of the problem which nature has solved, of constructing an optical instrument out of living and growing animal tissue, we cannot fail to be struck by the perfection of the dioptric apparatus of the eye as well as by its adaptation to the needs of the organism of which it forms a part.

Iris.—The importance of the iris as an adjustable diaphragm for cutting off side rays and thus securing good definition in near vision has been described in connection with the act of accommodation. Its other function of protecting the retina from an excess of light is no less important, and we must now consider how this pupillary adjustment may be studied and by what mechanism it is effected. The changes in the size of the pupil may be conveniently observed in man and animals by holding a millimeter scale in front of the eye and noticing the variations in the diameter of the pupil. It should be borne in mind that the iris, seen in this way, does not appear in its natural size and

position, but somewhat enlarged and bulged forward by the magnifying effect
of the cornea and the aqueous humor. The changes in one's own pupil may
be readily observed by noticing the varying size of the circle of light thrown
upon the retina when the eye is illuminated by a point of light held at the
anterior focus, as in the method above described for the study of intraocular
images.

The muscles of the iris are, except in birds, of the unstriped variety, and
are arranged concentrically around the pupil. Radiating fibres are also recog-
nized by many observers, though their existence has been called in question
by others. The circular or constricting muscles of the iris are under the con-
trol of the third pair of cranial nerves,
and are normally brought into activity
in consequence of light falling upon
the retina. This is a reflex phenom-
enon, the optic nerve being the affer-
ent, and the third pair, the ciliary
ganglion, and the short ciliary nerves
the efferent, channel, as indicated in
Figure 230. This reflex is in man
and many of the higher animals bi-
lateral—*i. e.* light falling upon one
retina will cause a contraction of both
pupils. This may readily be observed
in one's own eye when focally illumi-
nated in the manner above described.
Opening the other eye will, under
these conditions, cause a diminution,
and closing it an increase, in the size
of the circle of light. This bilateral
character is found to be dependent
upon the nature of the decussation of
the optic nerves, for in animals in
which the crossing is complete the
reflex is confined to the illuminated
eye. The arrangement of the fibres
in the optic commissure is in general
associated with the position of the
eyes in the head. When the eyes

Course of constrictor nerve-fibres ·······························
  "   dilator   "   -------------------

FIG. 230.—Diagrammatic representation of the
nerves governing the pupil (after Foster): *II*, optic
nerve; *l. g*, ciliary ganglion; *r. b*, its short root from
III, motor-oculi nerve; *sym*, its sympathetic root; *r. l*,
its long root from *V*, ophthalmo-nasal branch of oph-
thalmic division of fifth nerve; *s. c*, short ciliary
nerves; *l. c*, long ciliary nerves.

are so placed that they can both be directed to the same object, as in man
and many of the higher animals, the fibres of each optic nerve are usually
found to be distributed to both optic tracts, while in animals whose eyes
are in opposite sides of the head there is complete crossing of the optic nerves.
Hence it may be said that animals having binocular vision have in general
a bilateral pupillary reflex. The rule is, however, not without exceptions,
for owls, though their visual axes are parallel, have, like other birds, a com-

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plete crossing of the optic nerves, and consequently a unilateral pupillary reflex.[1]

A direct as well as a reflex constriction of the pupil under the influence of light has been observed in the excised eyes of eels, frogs, and some other animals. As the phenomenon can be seen in preparations consisting of the iris alone or of the iris and cornea together, it is evident that the light exerts its influence directly upon the tissues of the iris and not through an intraocular connection with the retina. The maximum effect is produced by the yellowish-green portion of the spectrum.

Antagonizing the motor oculi nerve in its constricting influence on the pupil is a set of nerve-fibres the function of which is to increase the size of the pupil. Most of these fibres seem to run their course from a centre which lies in the floor of the third ventricle not far from the origin of the third pair, through the bulb, the cervical cord, the anterior roots of the upper dorsal nerves, the upper thoracic ganglion, the cervical sympathetic nerve as far as the upper cervical ganglion; then through a branch which accompanies the internal carotid artery, passes over the Gasserian ganglion and joins the ophthalmic branch of the fifth pair; then through the nasal branch of the latter nerve and the long ciliary nerves to the eye[2] (see diagram, p. 769). These fibres appear to be in a state of tonic activity, for section of them in any part of their course (most conveniently in the cervical sympathetic) causes a contraction of the pupil which, on stimulation of the peripheral end of the divided nerve, gives place to a marked dilatation. Their activity can be increased in various ways. Thus dilatation of the pupil may be caused by dyspnea, violent muscular efforts, etc. Stimulation of various sensory nerves may also cause reflex dilatation of the pupil, and this phenomenon may be observed, though greatly diminished in intensity, after extirpation of the superior cervical sympathetic ganglion. It is therefore evident that the dilator nerves of the pupil do not have their course exclusively in the cervical sympathetic nerve.

Since the cervical sympathetic nerve contains vaso-constrictor fibres for the head and neck, it has been thought that its dilating effect upon the pupil might be explained by its power of causing changes in the amount of blood in the vessels of the iris. There is no doubt that a condition of vascular turgescence or depletion will tend to produce contraction or dilatation of the pupil, but it is impossible to explain the observed phenomena in this way, since the pupillary are more prompt than the vascular changes, and may be observed on a bloodless eye. Moreover, the nerve-fibres producing them are said to have a somewhat different course. Another explanation of the influence of the sympathetic on the pupil is that it acts by inhibiting the contraction of the sphincter muscles, and that the dilatation is simply an elastic reaction. But since it is posssible to produce local dilatation of the pupil by circumscribed stimulation at or near

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[1] Steinach : *Archiv für die gesammte Physiologie,* xlvii. 313.

[2] Langley : *Journal of Physiology,* xiii. p. 575. For the evidence of the existence of a "cilio-spinal" centre in the cord, see Steil and Langendorff: *Archiv für die gesammte Physiologie,* lviii. p. 155; also Schenck: *Ibid.,* lxii. p. 494.

the outer border of the iris, it seems more reasonable to conclude that the dilator nerves of the pupil act upon radial muscular fibres in the substance of the iris, in spite of the fact that the existence of such fibres has not been universally admitted.

Whatever view may be taken of the mechanism by which the sympathetic nerves influence the pupil, there is no doubt that the iris is under the control of two antagonistic sets of nerve-fibres, both of which are, under normal circumstances, in a state of tonic activity. Therefore, when the sympathetic nerve is divided the pupil contracts under the influence of the motor oculi, and section of the motor oculi causes dilatation through the unopposed influence of the sympathetic.

The movements of the iris, though performed by smooth muscles, are more rapid than those of smooth muscles found elsewhere—*e. g.* in the intestines and the arteries. The contraction of the pupil when the retina of the opposite eye is illuminated occupies about 0.3″; the dilatation when the light is cut off from the eye, about 3″ or 4″. The latter determination is, however, difficult to make with precision, since dilatation of the pupil takes place at first rapidly and then more slowly, so that the moment when the process is at an end is not easily determined. After remaining a considerable time in absolute darkness the pupils become enormously dilated, as has been shown by flashlight photographs taken under these conditions. In sleep, though the eyes are protected from the light, the pupils are strongly contracted, but dilate on stimulation of sensory nerves, even though the stimulation may be insufficient to rouse the sleeper.

Many drugs when introduced into the system or applied locally to the conjunctiva produce effects upon the pupil. Those which dilate it are known as *mydriatics,* those which contract it as *myotics.* Of the former class the most important is atropin, the alkaloid of the Atropa belladonna, and of the latter physostigmin, the alkaloid of the Calabar bean. In addition to their action upon the pupil, mydriatics paralyze the accommodation, thus focussing the eye for distant objects, while myotics, by producing a cramp of the ciliary muscle, adjust the eye for near vision. The effect on the accommodation usually begins later and passes off sooner than the affection of the pupil. Atropin seems to act by producing local paralysis of the terminations of the third pair of cranial nerves in the sphincter iridis and the ciliary muscle. In large doses it may also paralyze the muscle-fibres of the sphincter. With this paralyzing action there appears to be combined a stimulating effect upon the dilator muscles of the iris. The myotic action of physostigmin seems to be due to a local stimulation of the fibres of the sphincter of the iris.

Although in going from a dark room to a lighter one the pupil at first contracts, this contraction soon gives place to a dilatation, and in about three or four minutes the pupil usually regains its former size. In a similar manner the primary dilatation of the pupil caused by entering a dark room from a lighter one is followed by a contraction which usually restores the pupil to its original size within fifteen or twenty minutes. It is thus evident that the

amount of light falling upon the retina is not the only factor in determining the size of the pupil.   In fact, if the light acts for a sufficient length of time the pupil may have the same size under the influence of widely different degrees of illumination.[1]

This so-called "adaptation" of the eye to various amounts of light seems to be connected with the movements of the retinal pigment-granules and with the chemical changes of the visual purple, to be more fully described in connection with the physiology of the retina.

The Ophthalmoscope.—Under normal conditions the pupil of the eye appears as a black spot in the middle of the colored iris.   The cause of this dark appearance of the pupil is to be found in the fact that a source of light and the retina lie in the conjugate foci of the dioptric apparatus of the eye. Hence any light entering the eye that escapes absorption by the retinal pigment and is reflected from the fundus must be refracted back to the source from which it came.   The eye of an observer who looks at the pupil from another direction will see no light coming from it, and it will therefore appear to him black.   It is therefore evident that the essential condition for perceiving light coming from the fundus of the eye is that the line of vision of the observing eye shall be in the line of illumination.   This condition is fulfilled by means of instruments known as ophthalmoscopes.   The principles involved in the construction of the most common form of ophthalmoscope are illustrated diagrammatically in Figure 231.
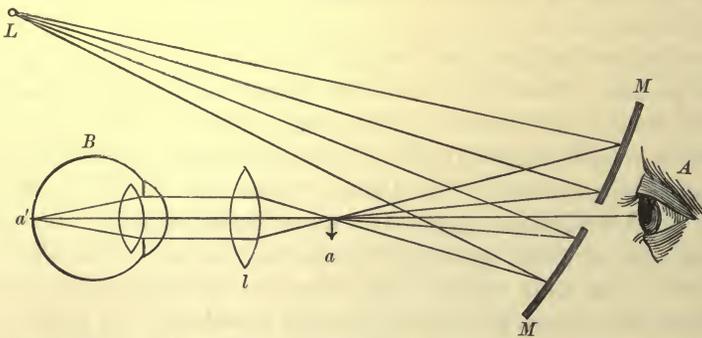
FIG. 231.—Diagram to illustrate the principles of a simple ophthalmoscope (after Foster).

The rays from a source of light L, after being brought to a focus at a by the concave perforated mirror M M, pass on and are rendered parallel by the lens l.   Then, entering the observed eye B, they are brought to a focus on the retina at a'.   Any rays which are reflected back from the part of the retina thus illuminated will follow the course of the entering rays and be brought to a focus at a.   The eye of an observer at A, looking through the hole in the mirror, will therefore see at a an inverted image of the retina, the observation of which may be facilitated by a convex lens placed immediately in front of the observer's eye.

[1] Schirmer : *Archiv für Ophthalmologie*, **xi.** 5.

The fundus of the eye thus observed presents a reddish background on which the retinal vessels are distinctly visible.

Retina.—Having considered the mechanism by which optical images of objects at various distances from the eye are formed upon the retina, we must next inquire what part of the retina is affected by the rays of light, and in what this affection consists. To the former of these questions it will be found possible to give a fairly satisfactory answer. With regard to the latter nothing positive is known.

The structure of the retina is exceedingly complicated, but, as very little is known of the functions of the ganglion cells and of the molecular and nuclear layers, it will suffice for the present purpose of physiological description to regard the retina as consisting of fibres of the optic nerve which are connected through various intermediate structures with the layer of rods and cones.
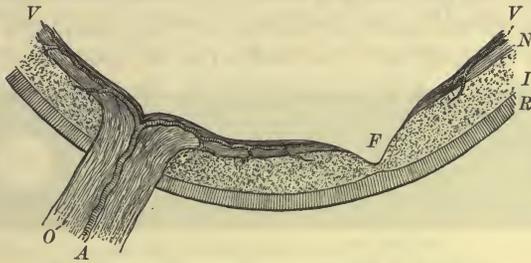
FIG. 232.—Diagrammatic representation of the retina.

Figure 232 is intended to show, diagrammatically, the mutual relation of these various portions of the retina in different parts of the eye, and is not drawn to scale. It will be observed that the optic nerve *O*, where it enters the eye, interrupts the continuity of the layer of rods and cones *R* and of the intermediate structures *I*. Its fibres spread themselves out in all directions, forming the internal layer of the retina *N*. The central artery of the retina *A* accompanying the optic nerve ramifies in the layer of nerve-fibres and in the immediately adjacent layers of the retina, forming a vascular layer *V*. In the fovea centralis *F* of the macula lutea (the centre of distinct vision) the layer of rods and cones becomes more highly developed, while the other layers of the retina are much reduced in thickness and the blood-vessels entirely disappear. This histological observation points strongly to the conclusion that the rods and cones are the structures which are essential to vision, and that in them are found the conditions for the conversion of the vibrations of the luminiferous ether into a stimulus for a nerve-fibre. This view derives confirmation from the observations on the retinal blood-vessels, for it is found that the distance between the vascular layer of the retina and the layer of rods and cones determined by histological methods corresponds with that which must exist between the vessels and the light-perceiving elements of the retina, as calculated from the apparent displacement of the shadow caused by given movements of the source of light used in studying intraocular images[1] as

[1] " Dimmer Verh. d. phys. Clubs zu Wien, 24 April, 1894," *Centralbl. für Physiologie*, 1894, 159.

described on p. 767. Another argument in favor of this view is found in the correspondence between the size of the smallest visible images on the retina and the diameter of the rods and cones. A double star can be recognized as double by the normal eye when the distance between the components corresponds to a visual angle of 60″. Two white lines on a black ground are seen to be distinct when the distance between them subtends a visual angle of 64″–73″. These angles correspond to a retinal image of 0.0044, 0.0046, and 0.0053 millimeter. Now, the diameter of the cones in the macula lutea, as determined by Kölliker, is 0.0045–0.0055 millimeter, a size which agrees well with the hypothesis that each cone when stimulated can produce a special sensation of light distinguishable from those caused by the stimulation of the neighboring cones. The existence of the so-called blind spot in the retina at the point of entrance of the optic nerve is sometimes regarded as evidence of the light-perceiving function of the rods and cones, but as the other layers of the retina, as well as the rods and cones, are absent at this point, and the retina here consists solely of nerve-fibres, it is evident that the presence of the blind spot

FIG. 233.—To demonstrate the blind spot.

only proves that the optic nerve-fibres are insensible to light. Figure 233 is intended to demonstrate this insensibility. For this purpose it should be held at a distance of about 23 centimeters from the eyes (*i. e.* about 3.5 times the distance between the cross and the round spot). If the left eye be closed and the right eye fixed upon the cross, the round spot will disappear from view, though it will become visible if the eye be directed either to the right or to the left of the cross, or if the figure be held either a greater or a less distance from the eye. The size and shape of the blind spot may readily be determined as follows : Fix the eye upon a definite point marked upon a sheet of white paper. Bring the black point of a lead pencil (which, except the point, has been painted white or covered with white paper) into the invisible portion of the field of vision and carry it outward in any direction until it becomes vis-

FIG. 234.—Form of the blind spot (Helmholtz).

ible. Mark upon the paper the point at which it just begins to be seen, and by repeating the process in as many different directions as possible the outline of the blind spot may be marked out. Figure 234 shows the shape of the blind spot determined by Helmholtz in his own right eye, *a* being the point of fixation of the eye, and the line *A B* being one-third of the distance between the eye and the paper. The irregularities of outline, as at

d, are due to shadows of the large retinal vessels. During this determination it is of course necessary that the head should occupy a fixed position with regard to the paper. This condition can be secured by holding firmly between the teeth a piece of wood that is clamped in a suitable position to the edge of the table. The diameter of the blind spot, as thus determined, has been found to correspond to a visual angle varying from 3° 39′ to 9° 47′, the average measurement being 6° 10′. This is about the angle that is subtended by the human face seen at a distance of two meters. Although a considerable portion of the retina is thus insensible to light, we are, in the ordinary use of the eyes, conscious of no corresponding blank in the field of vision. By what psychical operation we " fill up " the gap in our subjective field of vision caused by the blind spot of the retina is a question that has been much discussed without being definitely settled.

The above-mentioned reasons for regarding the rods and cones as the light-perceiving elements of the retina seem sufficiently conclusive. Whether there is any difference between the rods and the cones with regard to their light-perceiving function is a question which may be best considered in connection with a description of the qualitative modifications of light.

The histological relation between the various layers of the retina is still under discussion. According to recent observations of Cajal,[1] the connection between the rods and cones on the one side and the fibres of the optic nerve on the other is established in a manner which is represented diagrammatically in Figure 235. The prolongations of the bipolar cells of the internal nuclear layer *E* break up into fine fibres in the external molecular (or plexiform) layer *C.* Here they are brought into contact, though not into anatomical continuity, with the terminal fibres of the rods and cones. The inner prolongations of the same bipolar cells penetrate into the internal molecular (or plexiform) layer *F,* and there come into contact with the dendrites coming from the layer of ganglion-cells *G.* These cells are, in their turn, connected by their axis-cylinder processes with the fibres of the optic nerve. The bipolar cells which serve as connective links between the rods and the optic nerve-fibres are anatomically distinguishable (as indicated in the diagram)
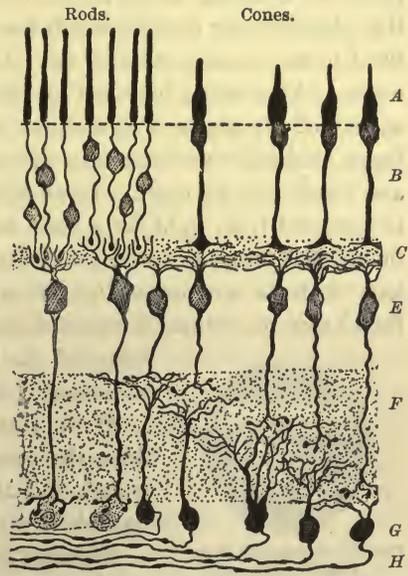
Fig. 235.—Diagrammatic representation of the structure of the retina (Cajal): *A,* layer of rods and cones; *B,* external nuclear layer; *C,* external molecular (or plexiform) layer; *E,* internal nuclear layer; *F,* internal molecular (or plexiform) layer; *G,* layer of ganglion-cells; *H,* layer of nerve-fibres.

[1] *Die Retina der Wirbelthiere,* Wiesbaden, 1894.

from those which perform the same function for the cones. Whatever be the precise mode of connection between the rods and cones and the fibres of the optic nerve, it is evident that each retinal element cannot be connected with the nerve-centres by a separate independent nerve-channel, since the retina contains many millions of rods and cones, while the optic nerve has only about 438,000 nerve-fibres,[1] though of course such a connection may exist in the fovea centralis, as Cajal has shown is probably the case in reptiles and birds.

Changes Produced in the Retina by Light.—We must now inquire what changes can be supposed to occur in the rods and cones under the influence of light by means of which they are able to transform the energy of the ether vibrations into a stimulus for the fibres of the optic nerve. Though in the present state of our knowledge no satisfactory answer can be given to this question, yet certain direct effects of light upon the retina have been observed which are doubtless associated in some way with the transformation in question.

The retina of an eye which has been protected from light for a considerable length of time has a purplish-red color, which upon exposure to light changes to yellow and then fades away. This bleaching occurs also in monochromatic light, the most powerful rays being those of the greenish-yellow portion of the spectrum—*i. e.* those rays which are most completely absorbed by the purplish-red coloring matter. A microscopic examination of the retina shows that this coloring matter, which has been termed *visual purple*, is entirely confined to the outer portion of the retinal rods and does not occur at all in the cones. After being bleached by light it is, during life, restored through the agency of the pigment epithelium, the cells of which, under the influence of light, send their prolongations inward to envelop the outer limbs of the rods and cones with pigment. If an eye, either excised or in its natural position, is protected from light for a time, and then placed in such a position that the image of a lamp or a window is thrown upon the retina for a time which may vary with the amount of light from seven seconds to ten minutes, it will be found that the retina, if removed and examined under red light, will show the

FIG. 236.—Optogram in eye of rabbit (Kühne).

image of the luminous object impressed upon it by the bleaching of the visual purple.

If the retina be treated with a 4 per cent. solution of alum, the restoration of the visual purple will be prevented, and the so-called " optogram " will be, as photographers say, " fixed." [2]

Figure 236 shows the appearance of a rabbit's retina on which the optogram of a window has been impressed.

Although the chemical changes in the visual purple under the influence of light seem, at first sight, to afford an explanation of the transformation of the vibrations of the luminiferous ether into a stimulation for the optic nerve, yet the fact that vision is most distinct in the fovea centralis of the retina, which,

[1] Salzer: *Wiener Sitzungsberichte,* 1880, Bd. lxxxi. S. 3.
[2] Kühne: *Untersuchungen a. d. phys. Inst. d. Universität Heidelberg,* i. 1.

as it contains no rods, is destitute of visual purple, makes it impossible to regard this coloring matter as essential to vision. The most probable theory of its function is perhaps that which connects it with the adaptation of the eye to varying amounts of light, as described on p. 772.

In addition to the above-mentioned movements of the pigment epithelium cells under the influence of light, certain changes in the retinal cones of frogs and fishes have been observed.[1] The change consists in a shortening and thickening of the inner portion of the cones when illuminated, but the relation of the phenomenon to vision has not been explained.

Like most of the living tissues of the body, the retina is the seat of electrical currents. In repose the fibres of the optic nerve are said to be positive in relation to the layer of rods and cones. When light falls upon the retina this current is at first increased and then diminished in intensity.

Sensation of Light.—Whatever view may be adopted with regard to the mechanism by which light is enabled to become a stimulus for the optic nerve, the fundamental fact remains that the retina (and in all probability the layer of rods and cones in the retina) alone supplies the conditions under which this transformation of energy is possible. But in accordance with the " law of specific energy " a sensation of light may be produced in whatever way the optic nerve be stimulated, for a stimulus reaching the visual centres through the optic nerve is interpreted as a visual sensation, in the same way that pressure on a nerve caused by the contracting cicatrix of an amputated leg often causes a painful sensation which is referred to the lost toes to which the nerve was formerly distributed. Thus local pressure on the eyeball by stimulating the underlying retina causes luminous sensations, already described as " phosphenes," and electrical stimulation of the eye as a whole or of the stump of the optic nerve after the removal of the eye is found to give rise to sensations of light.

Vibrations of the luminiferous ether constitute, however, the normal stimulus of the retina, and we must now endeavor to analyze the sensation thus produced. In the first place, it must be borne in mind that the so-called ether waves differ among themselves very widely in regard to their rate of oscillation. The slowest known vibrations of the ether molecules have a frequency of about 107,000,000,000,000 in a second, and the fastest a rate of about 40,000,000,000,000,000 in a second—a range, expressed in musical terms, of about eight and one-half octaves. All these ether waves are capable of warming bodies upon which they strike and of breaking up certain chemical combinations, the slowly vibrating waves being especially adapted to produce the former and the rapidly vibrating ones the latter effect. Certain waves of intermediate rates of oscillation—viz. those ranging between 392,000,000,-000,000 and 757,000,000,000,000 in a second—not only produce thermic and chemical effects, but have the power, when they strike the retina, of causing changes in the layer of rods and cones, which, in their turn, act as a stimulus to the optic nerve. The ether waves which produce these various phenomena

[1] Engelmann : *Archiv für die gesammte Physiologie,* xxxv. 498.

are often spoken of as heat rays, light rays, and actinic or chemical rays, but it must be remembered that the same wave may produce all three classes of phenomena, the effect depending upon the nature of the substance upon which it strikes. It will be observed that the range of vibrations capable of affecting the retina is rather less than one octave, a limitation which obviously tends to reduce the amount of chromatic aberration.

In this connection it is interesting to notice that the highest audible note is produced by about 40,000 sonorous impulses in a second. Between the highest audible note and the lowest visible color there is a gap of nearly thirty-four octaves in which neither the vibrations of the air nor those of the luminiferous ether affect our senses. Even if the slowly vibrating heat-rays which affect our cutaneous nerves are taken into account, there still remain over thirty-one octaves of vibrations, either of the air or of the luminiferous ether, which may be, and very likely are, filling the universe around us without in any way impressing themselves upon our consciousness.

Qualitative Modifications of Light.—All the ethereal vibrations which are capable of affecting the retina are transmitted with very nearly the same rapidity through air, but when they enter a denser medium the waves having a rapid vibration are retarded more than those vibrating more slowly. Hence when a ray of sunlight composed of all the visible ether waves strikes upon a

FIG. 237.—Diagram illustrating the dispersion of light by a prism.

plane surface of glass, the greater retardation of the waves of rapid vibration causes them to be more refracted than those of slower vibration, and if the glass has the form of a prism, as shown in Figure 237, this so-called "dispersion" of the rays is still further increased when the rays leave the glass, so that the emerging beam, if received upon a white surface, instead of forming a spot of white light, produces a band of color known as the solar spectrum. The colors of the spectrum, though commonly spoken of as seven in number, really form a continuous series from the extreme red to the extreme violet, these colors corresponding to ether vibrations have rates of 392,000,000,000,000 and 757,000,000,000,000 in 1 second, and wave lengths of 0.7667 and 0.3970 micromillimeters [1] respectively.

Colors, therefore, are sensations caused by the impact upon the retina of certain ether waves having definite frequencies and wave-lengths, but these are not the only peculiarities of the ether vibration which influence the retinal sensation. The energy of the vibration, or the *vis viva* of the vibrating molecule, determines the "intensity" of the sensation or the brilliancy of the light.[2]

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[1] One micromillimeter = 0.001 millimeter = one μ.

[2] The energy of vibration capable of producing a given subjective sensation of intensity varies with the color of the light, as will be later explained (see p. 786).

Furthermore, the sensation produced by the impact of ether waves of a definite length will vary according as the eye is simultaneously affected by a greater or less amount of white light. This modification of the sensation is termed its degree of "saturation," light being said to be completely saturated when it is "monochromatic" or produced by ether vibrations of a single wave-length.

The modifications of light which taken together determine completely the character of the sensation are, then, three in number—viz. : 1. Color, dependent upon rate of vibration or length of the ether wave ; 2. Intensity, dependent upon the energy of the vibration ; 3. Saturation, dependent upon the amount of white light mingled with the monochromatic light. These three qualitative modifications of light must now be considered in detail.

Color.—In our profound ignorance of the nature of the process by which, in the rods and cones, the movements of the ether waves are converted into a stimulus for the optic nerve-fibres, all that can be reasonably demanded of a color theory is that it shall present a logically consistent hypothesis to account for the sensations actually produced by the impact of ether waves of varying rates, either singly or combined, upon different parts of the retina. Some of the important phenomena of color sensation of which every color theory must take account may be enumerated as follows :

1. Luminosity is more readily recognized than color. This is shown by the fact that a colored object appears colorless when it is too feebly illuminated, and that a spectrum produced by a very feeble light shows variations of intensity with a maximum nearer than normal to the blue end, but no gradations of color. A similar lack of color is noticed when a colored object is observed for too short a time or when it is of insufficient size. In all these respects the various colors present important individual differences which will be considered later,

2. Colored objects seen with increasing intensity of illumination appear more and more colorless, and finally present the appearance of pure white. Yellow passes into white more readily than the other colors.

3. The power of the retina to distinguish colors diminishes from the centre toward the periphery, the various colors, in this respect also, differing materially from each other. Sensibility to red is lost at a short distance from the macula lutea, while the sensation of blue is lost only on the extreme lateral portions of the retina. The relation of this phenomenon to the distribution of the rods and cones in the retina will be considered in connection with the perception of the intensity of light.

Color-mixture.—Since the various spectral colors are produced by the dispersion of the white light of the sun, it is evident that white light may be reproduced by the reunion of the rays corresponding to the different colors, and it is accordingly found that if the colored rays emerging from a prism, as in Fig. 237, are reunited by suitable refracting surfaces, a spot of white light will be produced similar to that which would have been caused by the original beam of sunlight. But white light may be produced not only by the union of *all* the spectral colors, but by the union of certain selected colors in twos, threes,

fours, etc. Any two spectral colors which by their union produce white are said to be "complementary" colors. The relation of these pairs of complementary colors to each other may be best understood by reference to Figure 238.
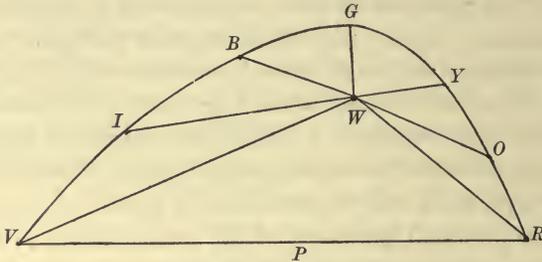
FIG. 238.—Color diagram.

Here the spectral colors are supposed to be disposed around a curved line, as indicated by their initial letters, and the two ends of the curve are united by a straight line, thus enclosing a surface having somewhat the form of a triangle with a rounded apex. If the curved edge of this surface be supposed to be loaded with weights proportionate to the luminosity of the different colors, the centre of gravity of the surface will be near the point W. Now, if a straight line be drawn from any point on the curved line through the point W and prolonged till it cuts the curve again, the colors corresponding to the two ends of this straight line will be complementary colors. Thus in Figure 238 it will be seen that the complementary color of red is bluish-green, and that of yellow lies near the indigo. It is also evident that the complementary color of green is purple, which is not a spectral color at all, but a color obtained by the union of violet and red. The union of a pair of colors lying nearer together than complementary colors produces an intermediate color mixed with an amount of white which is proportionate to the nearness of the colors to the complementary. Thus the union of red and yellow produces orange, but a less saturated orange than the spectral color. The union of two colors lying farther apart than complementary colors produces a color which borders more or less upon purple.

The mixing of colors to demonstrate the above-mentioned effects may be accomplished in three different ways :

1. By employing two prisms to produce two independent spectra, and then directing the colored rays which are to be united so that they will illuminate the same white surface.

2. By looking obliquely through a glass plate at a colored object placed behind it, while at the same time light from another colored object, placed in front of the glass, is reflected into the eye of the observer, as shown in Figure 239. Here the transmitted light from the colored object A and the reflected light from the colored object B enter the eye at C from the same direction, and are therefore united upon the retina.

3. By rotating before the eye a disk on which the colors to be united are

painted upon different sectors. This is most readily accomplished by using a number of disks, each painted with one of the colors to be experimented with, and each divided radially by a cut running from the centre to the circumference. The disks can then be lapped over each other and rotated together, and in this way two or more colors can be mixed in any desired proportions. This method of mixing colors depends upon the property of the retina to retain an impression after the stimulus causing it has ceased to act—a phenomenon of great importance in physiological optics, and one which will be further discussed in connection with the subject of "afterimages."

Fig. 239.—Diagram to illustrate color mixture by reflected and transmitted light (Helmholtz).

The physiological mixing of colors cannot be accomplished by the mixture of pigments or by allowing sunlight to pass successively through glasses of different colors, for in these cases rays corresponding to certain colors are absorbed by the medium through which the white light passes, and the phenomenon is the result of a process of subtraction and not addition. Light reaching the eye through red glass, for instance, looks red because all the rays except the red rays are absorbed, and light coming through green glass appears green for a similar reason. Now, when light is allowed to pass successively through red and green glass the only rays which pass through the red glass will be absorbed by the green. Hence no light will pass through the combination of red and green glass, and darkness results. But when red and green rays are mixed by any of the three methods above described the result of this process of addition is not darkness, but a yellow color, as will be understood by reference to the color diagram on p. 780. In the case of colored pigments similar phenomena occur, for here too light reaches the eye after rays of certain wave-lengths have been absorbed by the medium. This subject will be further considered in connection with color-theories.

Color-theories.—From what has been said of color-mixtures it is evident that every color sensation *may* be produced by the mixture of a number of other color sensations, and that *certain* color sensations—viz. the purples—can be produced *only* by the mixture of other sensations, since there is no single wave-length corresponding to them. Hence the hypothesis is a natural one that *all* colors are produced by the mixture in varying proportions of a certain number of fundamental colors, each of which depends for its production upon the presence in the retina of a certain substance capable of being affected (probably through some sort of a photo-chemical process) by light of a certain definite wave-length. A hypothesis of this sort lies at the basis of both the Young-Helmholtz and the Hering theories of color sensation.

The former theory postulates the existence in the retina of three substances capable of being affected by red, green, and violet rays, respectively—*i. e.* by the three colors lying at the three angles of the color diagram given on p. 780
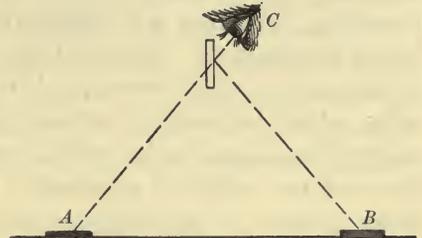
—and regards all other color sensations as produced by the simultaneous affection of two of these substances in varying proportions. Thus when a ray of blue light falls on the retina it stimulates the violet- and green-perceiving substances, and produces a sensation intermediate between the two, while simultaneous stimulation of the red- and green-perceiving substances produces the sensations corresponding to yellow and orange; and when the violet- and red-perceiving substances are affected at the same time, the various shades of purple are produced. Each of these three substances is, however, supposed to be affected to a slight extent by all the rays of the visible spectrum, a supposition which is rendered necessary by the fact that even the pure spectral colors do not appear to be perfectly saturated, as will be explained in connection with the subject of saturation. Furthermore, the disappearance of color when objects are very feebly or very brightly illuminated or when they are seen with the lateral portions of the retina (as described on p. 779) necessitates the additional hypotheses that these three substances are all equally affected by all kinds of rays when the light is of either very small or very great intensity or when it falls on the extreme lateral portions of the retina, and that they manifest their specific irritability for red, green, and violet rays respectively only in light of moderate intensity falling not too far from the fovea centralis of the retina.

The modifications of the Young-Hemholtz theory introduced by these subsidiary hypotheses greatly diminish the simplicity which was its chief claim to acceptance when originally proposed. Moreover, there will always remain a psychological difficulty in supposing that three sensations so different from each other as those of red, green, and violet can by their union produce a fourth sensation absolutely distinct from any of them—viz. white.

The fact that in the Hering theory this difficulty is obviated has contributed greatly to its acceptance by physiologists. In this theory the retina is supposed to contain three substances in which chemical changes may be produced by ether vibrations, but each of these substances is supposed to be affected in two opposite ways by rays of light which correspond to complementary color sensations. Thus in one substance—viz. the white-black visual substance—katabolic or destructive changes are supposed to be produced by all the rays of the visible spectrum, the maximum effect being caused by the yellow rays, while anabolic or constructive changes occur when no light at all falls upon the retina. The chemical changes of this substance correspond, therefore, to the sensation of luminosity as distinguished from color. In a second substance red rays are supposed to produce katabolic, and green rays anabolic changes, while a third substance is similarly affected by yellow and blue rays. These two substances are therefore spoken of as red-green and yellow-blue visual substances respectively.

It has been sometimes urged as an objection to this theory that the effect of a stimulus is usually katabolic and not anabolic. This is true with regard to muscular contraction, from the study of which phenomenon most of our knowledge of the effect of stimulation has been obtained, but it should be remem-

bered that observations on the augmentor and inhibitory cardiac nerves have shown us that nerve-stimulation may produce very contrary effects. There seems to be, therefore, no serious theoretical difficulty in supposing that light rays of different wave-lengths may produce opposite metabolic effects upon the substances in which changes are associated with visual sensations.

A more serious objection lies in the difficulty of distinguishing between the sensation of blackness, which, on Hering's hypothesis, must correspond to active anabolism of the white-black substance, and the sensation of darkness (such as we experience when the eyes have been withdrawn for some time from the influence of light), which must correspond to a condition of equilibrium of the white-black substance in which neither anabolism nor katabolism is occurring.

Another objection to the Hering theory is to be found in the results of experiments in comparing grays or whites produced by mixing different colored rays under varying intensities of light. The explanation given by Hering of the production of white through the mixture of blue and yellow or of red and green is that when either of these pairs of complementary colors is mixed the anabolic and the katabolic processes balance each other, leaving the corresponding visual substance in a condition of equilibrium. Hence, the white-black substance being alone stimulated, the result will be a sensation of white corresponding to the intensity of the katabolic process caused by the mixed rays. Now, it is found that when blue and yellow are mixed in certain proportions on a revolving disk a white can be produced which will, with a certain intensity of illumination, be undistinguishable from a white produced by mixing red and green. If, however, the intensity of the illumination is changed, it will be found necessary to add a certain amount of white to one of the mixtures in order to bring them to equality. On the theory that complementary colors produce antagonistic processes in the retina it is difficult to understand why this should be the case.

A color theory which is in some respects more in harmony with recent observations in the physiology of vision has been proposed by Mrs. C. L. Franklin. In this theory it is supposed that, in its earlier periods of development, the eye is sensitive only to luminosity and not to color—*i. e.* it possesses only a white-black or (to use a single word) a *gray*-perceiving substance which is affected by all visible light rays, but most powerfully by those lying near the middle of the spectrum. The sensation of gray is supposed to be dependent upon the chemical stimulation of the optic nerve-terminations by some product of decomposition of this substance.

In the course of development a portion of this gray visual substance becomes differentiated into three different substances, each of which is affected by rays of light corresponding to one of the three fundamental colors of the spectrum —viz. red, green, and blue. When a ray of light intermediate between two of the fundamental colors falls upon the retina, the visual substances corresponding to these two colors will be affected to a degree proportionate to the proximity of these two colors to that of the incident ray. Since this effect is

exactly the same as that which is produced when the retina is acted upon simultaneously by light of two fundamental colors, we are incapable of distinguishing in sensation between an intermediate wave-length and a mixture in proper amounts of two fundamental wave-lengths.

When the retina is affected by two or more rays of such wave-lengths that all three of the color visual substances are equally affected, the resulting decomposition will be the same as that produced by the stimulation of the gray visual substance out of which the color visual substances were differentiated, and the corresponding sensation will therefore be that of gray or white.

It will be noticed that the important feature of this theory is that it provides for the independent existence of the gray visual substance, while at the same time the stimulation of this substance is made a necessary result of the mixture of certain color sensations.

Color-blindness.—The fact that many individuals are incapable of distinguishing between certain colors—*i. e.* are more or less " color-blind "—is one of fundamental importance in the discussion of theories of color vision. By far the most common kind of color-blindness is that in which certain shades of red and green are not recognized as different colors. The advocates of the Young-Helmholtz theory explain such cases by supposing that either the red or the green perceiving elements of the retina are deficient, or, if present, are irritable, not by rays of a particular wave-length, but by all the rays of the visible spectrum. In accordance with this view these cases of color-blindness are divided into two classes—viz. the red-blind and the green-blind—the basis for the classification being furnished by more or less characteristic curves representing the variations in the luminosity of the visible spectrum as it appears to the different eyes. There are, however, cases which cannot easily be brought under either of these two classes. Moreover, it has been proved in cases of monocular color-blindness, and is admitted even by the defenders of the Helmholtz theory, that such persons see really only two colors—viz. blue and yellow. To such persons the red end of the spectrum appears a dark yellow, and the green portion of the spectrum has luminosity without color.

A better explanation of this sort of color-blindness is given in the Hering theory by simply supposing that in such eyes the red-green visual substance is deficient or wholly wanting, but the theory of Mrs. Franklin accounts for the phenomena in a still more satisfactory way ; for, by supposing that the differentiation of the primary gray visual substance has first led to the formation of a blue and a yellow visual substance, and that the latter has subsequently been differentiated into a red and a green visual substance, color-blindness is readily explained by supposing that this second differentiation has either not occurred at all or has taken place in an imperfect manner. It is, in other words, an arrest of development.

Cases of *absolute* color-blindness are said to occasionally occur. To such persons nature is colorless, all objects presenting simply differences of light and shade.

In whatever way color-blindness is to be explained, the defect is one of

considerable practical importance, since it renders those affected by it incapable of distinguishing the red and green lights ordinarily used for signals. Such persons are, therefore, unsuitable for employment as pilots, railway engineers, etc., and it is now customary to test the vision of all candidates for employment in such situations. It has been found that no satisfactory results can be reached by requiring persons to name colors which are shown them, and the chromatic sense is now commonly tested by what is known as the " Holmgren method," which consists in requiring the individual examined to select from a pile of worsteds of various colors those shades which seem to him to resemble standard skeins of green and pink. When examined in this way about 4 per cent. of the male and one-quarter of 1 per cent. of the female sex are found to be more or less color-blind. The defect may be inherited, and the relatives of a color-blind person are therefore to be tested with special care. Since females are less liable to be affected than males, it often happens that the daughters of a color-blind person, themselves with normal vision, have sons who inherit their grandfather's infirmity.

Although in all theories of color vision the different sensations are supposed to depend upon changes produced by the ether vibrations of varying rates acting upon different substances in the retina, yet it should be borne in mind that we have at present no proof of the existence of any such substances. The visual purple—or, to adopt Mrs. Franklin's more appropriate term, " the rod pigment"—was at one time thought to be such a substance, but for the reasons above given cannot be regarded as essential to vision.[1]

That a centre for color vision, distinct from the visual centre, exists in the cerebral cortex is rendered probable by the occurrence of cases of hemianopsia for colors, and also by the experiments of Heidenhain and Cohn on the influence of the hypnotic trance upon color-blindness.

Intensity.—The second of the above-mentioned qualitative modifications of light is its intensity, which is dependent upon the energy of vibrations of the molecules of the luminiferous ether. The sensation of luminosity is not, however, proportionate to the intensity of the stimulus, but varies in such a way that a given *increment* of intensity causes a greater difference in sensation with feeble than with strong illuminations. This phenomenon is illustrated by the disappearance of a shadow thrown by a candle in a darkened room on a sheet of white paper when sunlight is allowed to fall on the paper from the opposite direction. In this case the absolute difference in luminosity between the shadowed and unshadowed portions of the paper remains the same, but it becomes imperceptible in consequence of the increased total illumination.

Although our power of distinguishing *absolute* differences in luminosity diminishes as the intensity of the illumination increases, yet with regard to *relative* differences no such dependence exists. On the contrary, it is found within pretty wide limits that, whatever be the intensity of the illumination,

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[1] In a recently developed theory by Ebbinghaus (*Zeitschrift für Psychologie und Physiologie der Sinnesorgane*, v. 145) a physiological importance in relation to vision is attached to this substance in connection with other substances of a hypothetical character.

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it must be increased by a certain constant fraction of its total amount in order to produce a perceptible difference in sensation. This is only a special case of a general law of sensation known as Weber's law, which has been formulated by Foster as follows: "The smallest change in the magnitude of a stimulus which we can appreciate through a change in our sensation always bears the same proportion to the whole magnitude of the stimulus."

Luminosity of Different Colors.—When two sources of light having the same color are compared, it is possible to estimate their relative luminosity with considerable accuracy, a difference of about 1 per cent. of the total luminosity being appreciated by the eye. When the sources of light have different colors, much less accuracy is attainable, but there is still a great difference in the intensity with which rays of light of different wave-lengths affect the retina. We do not hesitate to say, for instance, that the maximum intensity of the solar spectrum is found in the yellow portion, but it is important to observe that the position of this maximum varies with the illumination. In a very brilliant spectrum the maximum shifts toward the orange, and in a feeble spectrum (such as may be obtained by narrowing the slit of the spectroscope) it moves toward the green. The curves in Figure 240 illus-
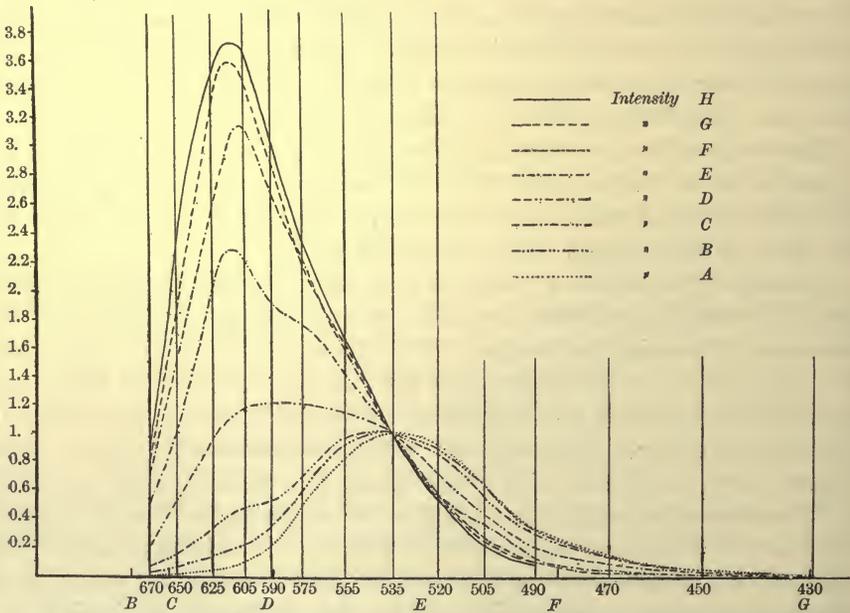
FIG. 240.—Diagram showing the distribution of the intensity of the spectrum as dependent upon the degree of illumination (König).

trate this shifting of the maximum of luminosity of the spectrum with varying intensities of illumination. The abscissas represent wave-lengths in millionths of a millimeter, and the ordinates the luminosity of the different colors as expressed by the reciprocal values of the width of the slit necessary to give to the color under observation a luminosity equal to that of an arbi-

trarily chosen standard. The curves from A to H represent the distribution of the intensity of light in the spectrum with eight different grades of illumination. This shifting of the maximum of luminosity in the spectrum explains the so-called " Purkinje's phenomenon "—viz. the changing relative values of colors in varying illumination. This can be best observed at nightfall, the attention being directed to a carpet or a wall-paper the pattern of which is made up of a number of different colors. As the daylight fades away the red colors, which in full illumination are the most intense, become gradually darker, and are scarcely to be distinguished from black at a time when the blue colors are still very readily distinguished.

Function of Rods and Cones.—The layer of rods and cones has thus far been spoken of as if all its elements had one and the same function. There is, however, some reason to suppose that the rods and cones have different functions. That color sensation and accuracy of definition are most perfect in the central portion of the retina is shown by the fact that when we desire to obtain the best possible idea of the form and color of an object we direct our eyes in such a way that the image falls upon the fovea centralis of the retina. The luminosity of a faint object, however, seems greatest when we look not directly at it, but a little to one side of it. This can be readily observed when we look at a group of stars, as, for example, the Pleiades. When the eyes are accurately directed to the stars so as to enable us to count them, the total luminosity of the constellation appears much less than when the eyes are directed to a point a few degrees to one side of the object. Now, an examination of the retina shows only cones in the fovea centralis. In the immediately adjacent parts a small number of rods are found mingled with the cones. In the lateral portions of the retina the rods are relatively more numerous than the cones, and in the extreme peripheral portions the rods alone exist. Hence this phenomenon is readily explained on the supposition that the rods are a comparatively rudimentary form of visual apparatus taking cognizance of the existence of light with special reference to its varying intensity, and that the cones are organs specially modified for the localization of stimuli and for the perception of differences of wave-lengths. The view that the rods are specially adapted for the perception of luminosity and the cones for that of color derives support from the fact that in the retina of certain nocturnal animals—*e. g.* bats and owls—rods alone are present. This theory has been further developed by Von Kries,[1] who in a recent article describes the rods as differing from the cones in the following respects : (1) They are color-blind—*i. e.* they produce a sensation of simple luminosity whatever be the wave-length of the light-ray falling on them ; (2) they are more easily stimulated than the cones, and are particularly responsive to light-waves of short wave-lengths ; (3) they have the power of adapting themselves to light of varying intensity.

On this theory it is evident that we must get the sensation of white or

[1] *Zeitschrift für Psychologie und Physiologie der Sinnesorgane,* ix. 81.

colorless light in two different ways: (1) In consequence of the stimulation of the rods by any sort of light-rays, and (2) in consequence of the stimulation of the cones by certain combinations of light-rays—*i. e.* complementary colors. In this double mode of white perception lies perhaps the explanation of the effect of varying intensity of illumination upon the results of color-mixtures which has been above alluded to (see p. 783) as an objection to the Hering theory. The so-called "Purkinje's phenomenon," described on p. 787, is readily explained in accordance with this theory, for, owing to the greater irritability of the rods, the importance of these organs, as compared with the cones, in the production of the total visual sensation is greater with feeble than with strong illumination of the field of vision. At the same time, the power of the rods to respond particularly to light-rays of short wave-length will cause a greater apparent intensity of the colors at the blue than at the red end of the spectrum. In this connection it is interesting to note that the phenomenon is said not to occur when the observation is limited to the fovea centralis, where cones alone are found.[1]

Saturation.—The degree of saturation of light of a given color depends, as above stated, upon the amount of white light mixed with it. The quality of light thus designated is best studied and appreciated by means of experiments with rotating disks. If, for instance, a disk consisting of a large white and a small red sector be rapidly rotated, the effect produced is that of a pale pink color. By gradually increasing the relative size of the red sector the pink color becomes more and more saturated, and finally when the white sector is reduced to zero the maximum of saturation is produced. It must be borne in mind, however, that no pigments represent completely saturated colors. Even the colors of the spectrum do not produce a sensation of absolute saturation, for, whatever theory of color vision be adopted, it is evident that all the color-perceiving elements of the retina are affected *more or less* by all the rays of light. Thus when rays of red light fall upon the retina they will stimulate not only the red-perceiving elements, but to a slight extent also (to use the language of the Helmholtz theory) the green- and violet-perceiving elements of the retina. The effect of this will be that of mixing a small amount of white with a large amount of red light—*i. e.* it will produce the sensation of incompletely saturated red light. This dilution of the sensation can be avoided only by previously exhausting the blue- and green-perceiving elements of the retina in a manner which will be explained in connection with the phenomena of after-images.

Retinal Stimulation.—Whenever by a stimulus applied to an irritable substance the potential energy there stored up is liberated the following phenomena may be observed: 1. A so-called latent period of variable duration during which no effects of stimulation are manifest; 2. A very brief period during which the effect of the stimulation reaches a maximum; 3. A period of continued stimulation during which the effect diminishes in consequence of the using up of the substance containing the potential energy—*i. e.* a period

[1] Von Kries: *Centralblatt für Physiologie,* 1896, i.

of fatigue ; 4. A period after the stimulation has ceased in which the effect slowly passes away.
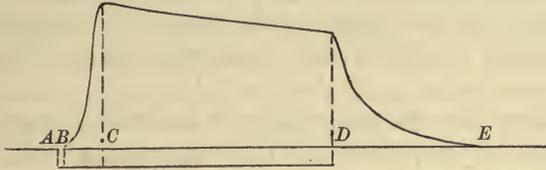
Fig. 241.—Diagram showing the effect of stimulation of an irritable substance.

The curve drawn by a muscle in tetanic contraction, as shown in Figure 241, illustrates this phenomenon. Thus, if $A\ D$ represents the duration of the stimulation, $A\ B$ indicates the latent period, $B\ C$ the period of contraction, $C\ D$ the period of fatigue under stimulation, and $D\ E$ the after-effect of stimulation showing itself as a slow relaxation. When light falls upon the retina corresponding phenomena are to be observed.

Latent Period.—That there is a period of latent sensation in the retina (*i. e.* an interval between the falling of light on the retina and the beginning of the sensation) is, judging from the analogy of other parts of the nervous system, quite probable, though its existence has not been demonstrated.

Rise to Maximum of Sensation.—The rapidity with which the sensation of light reaches its maximum increases with the intensity of the light and varies with its color, red light producing its maximum sensation sooner than green and blue. Consequently, when the image of a white object is moved across the retina it will appear bordered by colored fringes, since the various constituents of white light do not produce their maximum effects at the same time. This phenomena can be readily observed when a disk on which a black and a white spiral band alternate with each other (as shown in Figure 242, *A*) is rotated before the eyes. The white band as its image moves out-
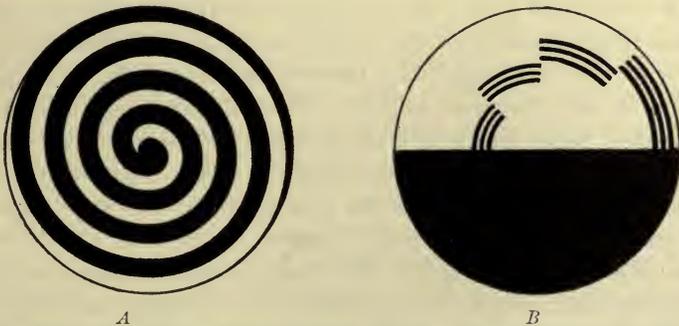
Fig. 242.—Disks to illustrate the varying rate at which colors rise to their maximum of sensation.

ward or inward over the retinal surface appears bordered with colors which vary with the rate of rotation of the disk and with the amount of exhaustion of the retina. Chromatic effects due to a similar cause are also to be seen when a disk, such as is shown in Figure 242, *B* (known as Benham's spectrum

top), is rotated with moderate rapidity. The concentric bands of color appear in reverse order when the direction of rotation is reversed. The apparent movement of colored figures on a background of a different color when the eye moves rapidly over the object or the object is moved rapidly before the eye seems to depend upon this same retinal peculiarity. The phenomenon may be best observed when small pieces of bright-red paper are fastened upon a bright-blue sheet and the sheet gently shaken before the eyes. The red figures will appear to move upon the blue background. The effect may be best observed in a dimly-lighted room.

In this connection should be mentioned the phenomenon of "recurrent images" or "oscillatory activity of the retina."[1] This may be best observed when a black disk containing a white sector is rotated at a rate of about one revolution in two seconds. If the disk is brightly illuminated, as by sunlight, and the eye fixed steadily upon the axis of rotation, the moving white sector seems to have a shadow upon it a short distance behind its advancing border, and this shadow may be followed by a second fainter, and even by a third still fainter shadow, as shown in Figure 243. The distance of the shadows from each other and from the edge of the sector increases with the rate of rotation of the disk and corresponds to a time interval of about 0.015″. It thus appears that when light is suddenly thrown upon the retina the sensation does not at once rise to its maximum, but reaches this point by a sort of vibratory movement. The apparent duplication of a single very brief retinal stimulation, as that caused by a flash of lightning, may perhaps be a phenomenon of the same sort.

FIG. 243.—To illustrate the oscillatory activity of the retina (Charpentier).

Fatigue of Retina.—When the eye rests steadily upon a uniformly illuminated white surface (*e. g.* a sheet of white paper), we are usually unconscious of any diminution in the intensity of the sensation, but it can be shown that the longer we look at the paper the less brilliant it appears, or, in other words, that the retina really becomes fatigued. To do this it is only necessary to place a disk of black paper on the white surface and to keep the eyes steadily fixed for about half a minute upon the centre of the disk. Upon removing the disk without changing the direction of the eyes a round spot will be seen on the white paper in the place previously occupied by the disk. On this spot the whiteness of the paper will appear much more intense than on the neighboring portion of the sheet, because we are able in this experiment to bring into direct contrast the sensations produced by a given amount of light upon a fresh and a fatigued portion of the retina.[2]

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[1] Charpentier : *Archives de Physiologie*, 1892, pp. 541, 629; and 1896, p. 677.

[2] Although the retina is here spoken of as the portion of the visual apparatus subject to fatigue, it should be borne in mind that we cannot, in the present state of our knowledge, discriminate between retinal fatigue and exhaustion of the visual nerve-centres.

The rapidity with which the retina becomes fatigued varies with the color of the light. Hence when intense white light falls upon the retina, as when we look at the setting sun, its disk seems to undergo changes of color as one or another of the constituents of its light becomes, through fatigue, less and less conspicuous in the combination of rays which produces the sensation of white.

The After-effect of Stimulation.—The persistence of the sensation after the stimulus has ceased causes very brief illuminations (*e. g.* by an electric spark) to produce distinct effects. On this phenomenon depends also the above-described method of mixing colors on a revolving disk, since a second color is thrown upon the retina before the impression produced by the first color has had time enough to become sensibly diminished. The interval at which successive stimulations must follow each other in order to produce a uniform sensation (a process analogous to the tetanic stimulation of a muscle) may be determined by rotating a disk, such as represented in Figure 244, and ascertaining at what speed the various rings produce a uniform sensation of gray. The interval varies with the intensity of the illumination from 0.1″ to 0.033″. The duration of the after-effect depends also upon the length of the stimulation and upon the color of the light producing it, the most persistent effect being produced by the red rays. In this connection it is interesting to

Fig. 244.—Disk to illustrate the persistence of retinal sensation (Helmholtz).

note that while with the rapidly vibrating blue rays a less intense illumination suffices to stimulate the eye, the slowly vibrating red rays produce the more permanent impression.

After-images.—When the object looked at is very brightly illuminated the impression upon the retina may be so persistent that the form and color of the object are distinctly visible for a considerable time after the stimulus has ceased to act. This appearance is known as a " positive after-image," and can be best observed when we close the eyes after looking at the sun or other bright source of light. Under these circumstances we perceive a brilliant spot of light which, owing to the above-mentioned difference in the persistence of the impressions produced by the various colored rays, rapidly changes its color, passing generally through bluish green, blue, violet, purple, and red, and then disappearing. This phenomenon is apt to be associated with or followed by another effect known as a " negative after-image." This form of after-image is much more readily observed than the positive variety, and seems to depend upon the fatigue of the retina. It is distinguished from the positive after-image by the fact that its color is always complementary to that of the object causing it. In the experiment to demonstrate the fatigue of the retina, described on p. 790, the white spot which appears after the black disk is withdrawn is the " negative after-image " of the disk, white being complementary to black. If a

colored disk be placed upon a sheet of white paper, looked at attentively for a few seconds, and then withdrawn, the eye will perceive in its place a spot of light of a color complementary to that of the disk. If, for example, the disk be yellow, the yellow-perceiving elements of the retina become fatigued in looking at it. Therefore when the mixed rays constituting white light are thrown upon the portion of the retina which is thus fatigued, those rays which produce the sensation of yellow will produce less effect than the other rays for which the eye has not been fatigued. Hence white light to an eye fatigued for yellow will appear blue.

If the experiment be made with a yellow disk resting on a sheet of blue paper, the negative after-image will be a spot on which the blue color will appear (1) more *intense* than on the neighboring portions of the sheet, owing to the blue-perceiving elements of that portion of the retina not being fatigued; (2) more *saturated*, owing to the yellow-perceiving elements being so far exhausted that they no longer respond to the slight stimulation which is produced when light of a complementary color is thrown upon them, as has been explained in connection with the subject of saturation.

Contrast.—As the eye wanders from one part of the field of vision to another it is evident that the sensation produced by a given portion of the field will be modified by the amount of fatigue produced by that portion on which the eye has last rested, or, other words, the sensation will be the result
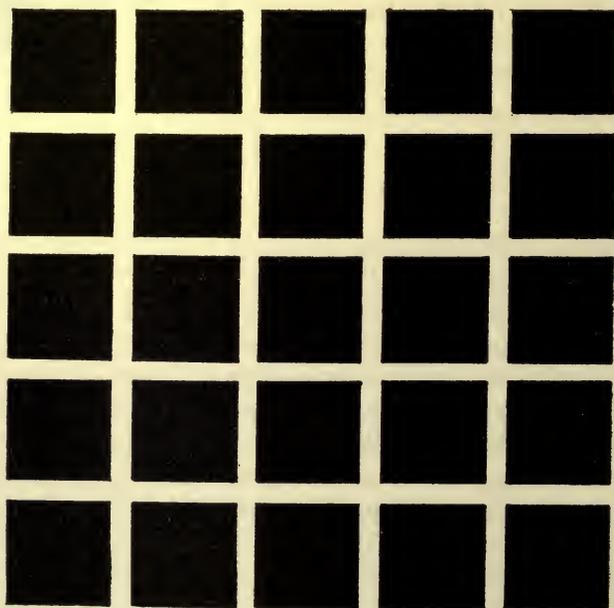
Fig. 245.—To illustrate the phenomenon of contrast.

of the stimulation by the object looked at combined with the negative after-image of the object previously observed. The effect of this combination is to produce the phenomenon of successive *contrast*, the principle of which may be thus stated : Every part of the field of vision appears lighter near a darker

part and darker near a lighter part, and its color seen near another color approaches the complementary color of the latter. A contrast phenomenon similar in its effects to that above described may be produced under conditions in which negative after-images can play no part. This kind of contrast is known as *simultaneous contrast*, and may perhaps be explained on the theory that a stimulation of a given portion of the retina produces in the neighboring portions an effect to some extent antagonistic to that caused by direct stimulation.

A good illustration of the phenomenon of contrast is given in Figure 245, in which black squares are separated by white bands which at their points of intersection appear darker than where they are bordered on either side by the black squares.

A black disk on a yellow background seen through white tissue-paper appears blue, since the white paper makes the black disk look gray and the yellow background pale yellow. The gray disk in contrast to the pale yellow around it appears blue.

The phenomenon of *colored shadows* also illustrates the principle of contrast. These may be observed whenever an object of suitable size and shape is placed upon a sheet of white paper and illuminated from one direction by daylight and from another by gaslight. Two shadows will be produced, one of which will appear yellow, since it is illuminated only by the yellowish gaslight, while the other, though illuminated by the white light of day, will appear blue in contrast to the yellowish light around it.

Space-perception.—Rays of light proceeding from every point in the field of vision are refracted to and stimulate a definite point on the surface of the retina, thus furnishing us with a local sign by which we can recognize the position of the point from which the light proceeds. Hence the size and shape of an optical image upon the retina enable us to judge of the size of the corresponding object in the same way that the cutaneous terminations of the nerves of touch enable us to judge of the size and shape of an object brought in contact with the skin. This spatial perception is materially aided by the muscular sense of the muscles moving the eyeball, for we can obtain a much more accurate idea of the size of an object if we let the eye rest in succession upon its different parts than if we gaze fixedly at a given point upon its surface. The conscious effort associated with a given amount of muscular motion gives, in the case of the eye, a measure of distance similar to that secured by the hand when we move the fingers over the surface of an object to obtain an idea of its size and shape.

The perception of space by the retina is limited to space in two dimensions —*i. e.* in a plane perpendicular to the axis of vision. Of the third dimension in space—*i. e.* of distance from the eye—the retinal image gives us no knowledge, as may be proved by the study of after-images. If an after-image of any bright object—*e. g.* a window—be produced upon the retina in the manner above described and the eye be then directed to a sheet of paper held in the hand, the object will appear outlined in miniature upon the surface of the paper. If, however, the eye be directed to the ceiling of the room, the object

will appear enlarged and at a distance corresponding to that of the surface looked at. Hence one and the same retinal image may, under different circumstances, give rise to the impression of objects at different distances. We must therefore regard the perception of distance not as a direct datum of vision, but, as will be later explained, a matter of visual judgment.

When objects are of such a shape that their images may be thrown successively upon the same part of the retina, it is possible to judge of their relative size with considerable accuracy, the retinal surface serving as a scale to which the images are successively applied. When this is not the case, the error of judgment is much greater. We can compare, for instance, the relative length of two vertical or of two horizontal lines with a good deal of precision, but in comparing a vertical with a horizontal line we are liable to make a considerable error. Thus it is difficult to realize that the vertical and the horizontal lines in Figure 246 are of the same length. The error consists in an over-estimation of the length of the vertical lines relatively to horizontal ones, and appears to depend, in part at any rate, upon the small size of the superior rectus muscle relatively to the other muscles of the eye. The difference amounts to 30–45 per cent. in weight and 40–53 per cent. in area of cross section. It is evident, therefore, that a given motion of the eye in the upward direction will require a more powerful contraction of the weaker muscle concerned in the movement than will be demanded of the stronger muscles moving the eye laterally to an equal amount.

Fig. 246.—To illustrate the over-estimation of vertical lines.

Hence we judge the upward motion of the eye to be greater because to accomplish it we make a greater effort than is required for a horizontal movement of equal extent.

The position of the vertical line bisecting the horizontal one (in Fig. 246) aids the illusion, as may be seen by turning the page through 90°, so as to bring the bisected line into a vertical position, or by looking at the lines in Figure 247, in which the illusion is much less marked than in Figure 246.

The tendency to over-estimate the length of vertical lines is also illustrated by the error commonly made in supposing the height of the crown of an ordinary silk hat to be greater than its breadth.

Fig. 247.—To illustrate the over-estimation of vertical lines.

Irradiation.—Many other circumstances affect the accuracy of the spatial perception of the retina. One of the most important of these is the intensity of the illumination. All brilliantly illuminated objects appear larger than feebly illuminated ones of the same size, as is

well shown by the ordinary incandescent electric lamp, the delicate filament of which is scarcely visible when cold, but when intensely heated by the electric current glows as a broad band of light. The phenomenon is known as "irradiation," and seems to depend chiefly upon the above-described imperfections in the dioptric apparatus of the eye, in consequence of which points of light produce small circles of dispersion on the retina and bright objects produce
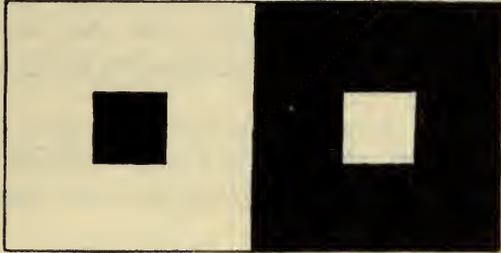
FIG. 248.—To illustrate the phenomenon of irradiation.

images with imperfectly defined outlines. The white square surrounded by black and the black square surrounded by white (Figure 248), being of the same size, would in an ideally perfect eye produce images of the same size on the retina, but owing to the imperfections of the eye the images are not sharply
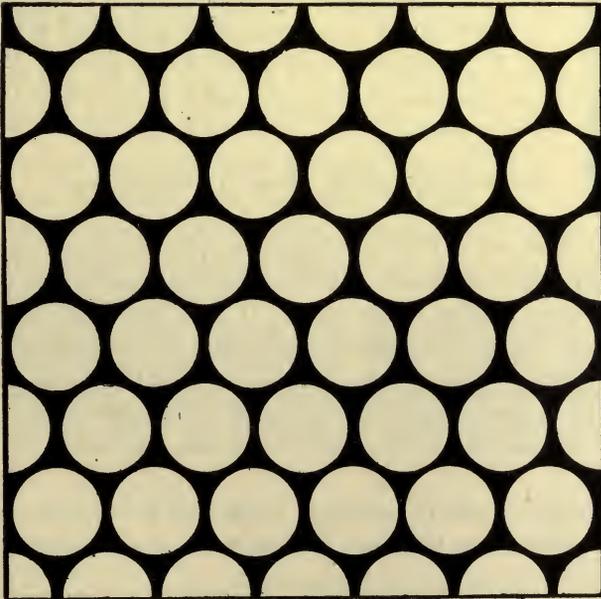
FIG. 249.—To illustrate the phenomenon of irradiation.

defined, and the white surfaces consequently appear to encroach upon the darker portions of the field of vision. Hence the white square looks larger than the black one, the difference in the apparent size depending upon the intensity of the illumination and upon the accuracy with which the eye can be accommo-

dated for the distance at which the objects are viewed. The effect of irradiation is most manifest when the dark portion of the field of vision over which the irradiation takes place has a considerable breadth. Thus the circular white spots in Figure 249, when viewed from a distance of three or four meters, appear hexagonal, since the irradiation is most marked into the triangular dark space between three adjacent circles. A familiar example of the effect of irradiation is afforded by the appearance of the new moon, whose sun-illuminated crescent seems to be part of a much larger circle than the remainder of the disk, which shines only by the light reflected upon it from the surface of the earth.

Subdivided Space.—A space subdivided into smaller portions by intermediate objects seems more extensive than a space of the same size not so subdivided. Thus the distance from A to B (Fig. 250) seems longer than that from
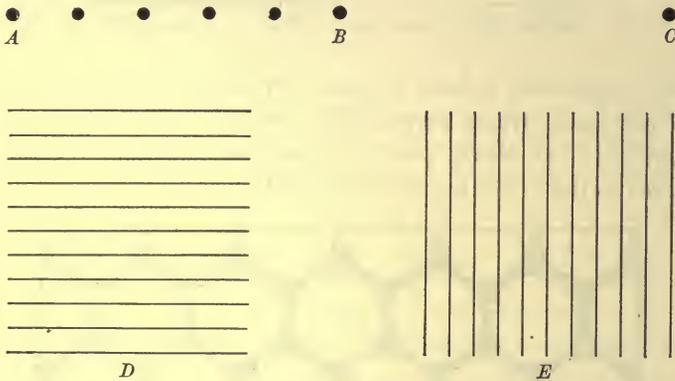
FIG. 250.—To illustrate the illusion of subdivided space.

B to C, though both are of the same length, and for the same reason the square D seems higher than it is broad, and the square E broader than it is high, the illusion being more marked in the case of D than in the case of E, because, as above explained, vertical distances are, as a rule, over-estimated.

The explanation of this illusion seems to be that the eye in passing over a subdivided line or area recognizes the number and size of the subdivisions, and thus gets an impression of greater total size than when no subdivisions are present.

A good example of this phenomenon is afforded by the apparently increased extent of a meadow when the grass growing on it is cut and arranged in haycocks.[1]

The relations of lines to each other gives rise to numerous illusions of spatial perception, among the most striking of which are those afforded by the so-called "Zöllner's lines," an example of which is given in Figure 251. Here

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[1] It is interesting to note that a similar illusion has been observed when an interval of time subdivided by audible signals is compared with an equal interval not so subdivided (Hall and Jastrow: *Mind*, xi. 62).

the horizontal lines, though strictly parallel to each other, seem to diverge and converge alternately, their apparent direction being changed toward greater per-
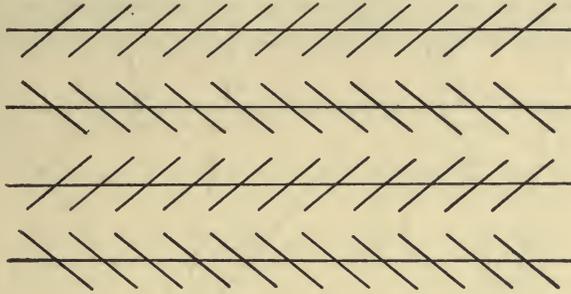
FIG. 251.—Zöllner's lines.

pendicularity to the short oblique lines crossing them. This illusion is to be explained in part by the tendency of the eye to over-estimate the size of acute and to under-estimate that of obtuse angles—a tendency which also affords a partial explanation of the illusion in Figure 252, where the line *d* is the real and the line *f* the apparent continuation of the line *a*. The illusion in Zöllner's figures is more marked when the figure is so held that the long parallel lines make an angle of about 45° with the horizon, since in this position the eye appreciates their real position less accurately than when they are vertical or horizontal. It is diminished, but does not disappear, when the eye, instead of being allowed to wander over the figure, is fixed upon any one point of the field of vision. Hence the motions of the eye must be regarded as a factor in, but not the sole cause of, the illusion.
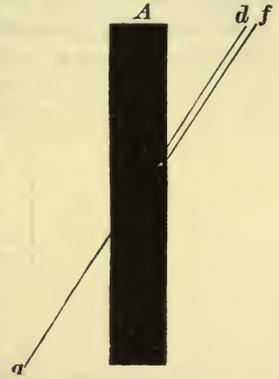
FIG. 252.—To illustrate illusion of space-perception.

Our estimate of the size of given lines, angles, and areas is influenced by neighboring lines, angles, and areas with which they are compared. This influence is sometimes exerted in accordance with the principle of contrast, and tends to make a given extension appear larger in presence of a smaller,

FIG. 253.—To illustrate contrast in space-perception (Müller-Lyer).

and smaller in presence of a larger extension. This effect is illustrated in Figure 253, in which the middle portion of the shorter line appears larger than the corresponding portion of the longer line, in Figure 254, in which a similar effect is observed in the case of angles, and in Figure 255, in which

the space between the two squares seems smaller than that between the two oblong figures.

In some case, however, an influence of the opposite sort[1] seems to be
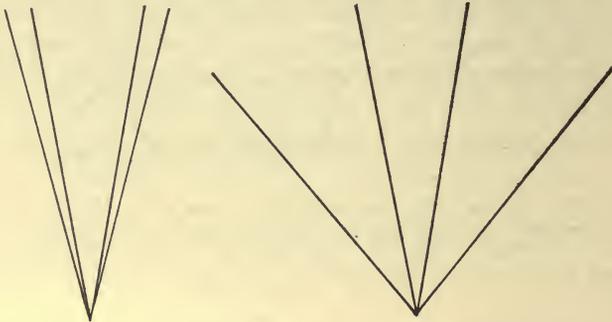
FIG. 254.—To illustrate contrast in space-perception (Müller-Lyer).

exerted, as is shown in Figure 256, in which the middle one of three parallel lines seems longer when the outside lines are longer, and shorter when they are shorter than it is itself, and in Figure 257, where a circle appears larger
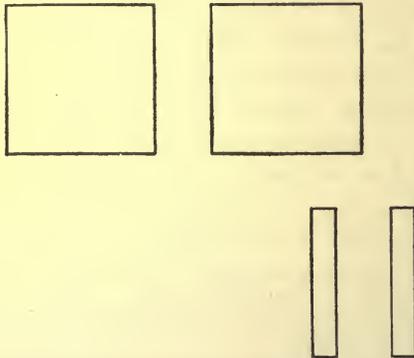
FIG. 255.—To illustrate contrast in space-perception (Müller-Lyer).

if surrounded by a circle larger than itself, and smaller if a smaller circle is shown concentrically within it.

Lines meeting at an angle appear longer when the included angle is large
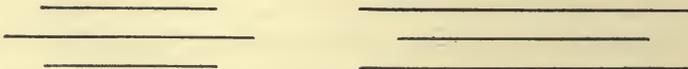
FIG. 256.—To illustrate so-called "confluxion" in space-perception (Müller-Lyer).

than when it is small, as is shown in Figure 258. This influence of the included angle affords a partial explanation of the illusion shown in Figure 259, where the horizontal line at *B* seems longer than at *A* ; but the distance

[1] For this influence the name "confluxion" has been proposed by Müller-Lyer, from whose article in the *Archiv für Physiologie*, 1889, Sup. Bd., the above examples are taken.

between the extremities of the oblique lines seems also to affect our estimate
of the horizontal line in the same way as the outside lines in Figure 256
influence our judgment of the length of the line between them.

Perception of Distance.—The retinal image gives us, as we have seen,
no *direct* information as to the distance of the object from the eye. This
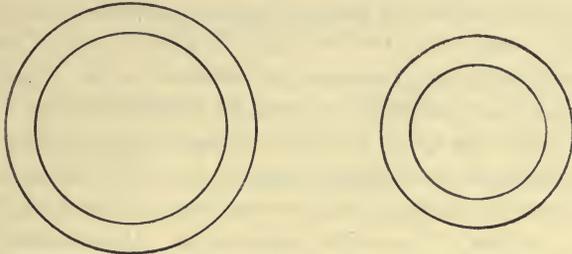
FIG. 257.—To illustrate so-called "confluxion" in space-perception (Müller-Lyer).

knowledge is, however, quite as important as that of position in a plane per-
pendicular to the line of vision, and we must now consider in what way it is
obtained. The first fact to be noted is that there is a close connection between
the judgments of distance and of actual size. A retinal image of a given
size may be produced by a small object near the eye or by a large one at a

FIG. 258.—To illustrate the influence of angles upon the apparent length of lines (Müller-Lyer).

distance from it. Hence when we know the actual size of any object (as, for
example, a human figure) we judge of its distance by the size of its image on
the retina. Conversely, our estimate of the actual size of an object will
depend upon our judgment of its distance. The fact that children constantly
misjudge both the size and distance of objects shows that the knowledge of

FIG. 259.—Illusion of space-perception.

this relation is acquired only by experience. If circumstances mislead us
with regard to the distance of an object, we necessarily make a corresponding
error with regard to its size. Thus, objects seen indistinctly, as through a fog,
are judged to be larger, because we suppose them to be farther off, than they
really are. The familiar fact that the moon seems to be larger when near the
horizon than when near the zenith is also an illustration of this form of illu-

sion. When the moon is high above our heads we have no means of esti-
mating its distance from us, since there are no intervening objects with which
we can compare it. Hence we judge it to be nearer than when, seen on the
horizon, it is obviously farther off than all terrestrial objects. Since the size
of the retinal image of the moon is the same in the two cases, we reconcile
the sensation with its apparent greater distance when seen on the horizon by
attributing to the moon in this position a greater actual size.

If the retinal image have the form of a familiar object of regular shape—
e. g. a house or a table—we interpret its outlines in the light of experience
and distinguish without difficulty between the nearer and more remote parts of
the object. Even the projection of the outlines of such an object on to a plane
surface (*i. e.* a perspective drawing) suggests the real relations of the different
parts of the picture so strongly that we recognize at once the relative distances
of the various portions of the object represented. How powerfully a familiar
outline can suggest the form and relief usually associated with it is well illus-
trated by the experiment of looking into a mask painted on its *interior* to
resemble a human face. In this case the familiar outlines of a human face
are brought into unfamiliar association with a receding instead of a projecting
form, but the ordinary association of these outlines is strong enough to force
the eye to see the hollow mask as a projecting face.[1] The fact that the pro-
jecting portions of an object are usually more brightly illuminated than the
receding or depressed portions is of great assistance in determining their rela-
tive distance. This use of shadows as an aid to the perception of relief pre-
supposes a knowledge of the direction from which the light falls on an object,
and if we are deceived on the latter we draw erroneous conclusions with
regard to the former point. Thus, if we look at an embossed letter or figure
through a lens which makes it appear inverted the accompanying reversal of
the shadows will cause the letter to appear depressed. The influence of
shadows on our judgment of relief is, however, not so strong as that of the
outline of a familiar object. In a case of conflicting testimony the latter
usually prevails, as, for example, in the above-mentioned experiment with the
mask.

Aided by these peculiarities of the retinal picture, the mind interprets it as
corresponding in its different parts to points at different distances from the eye,
and it is interesting to notice that painters, whose work, being on a plane sur-
face, is necessarily in all its parts at the same distance from the eye, use similar
devices in order to give depth to their pictures. Distant hills are painted with
indistinct outlines to secure what is called "aërial perspective." Figures of
men and animals are introduced in appropriate dimensions to suggest the dis-
tance between the foreground and the background of the picture. Landscapes
are painted preferably by morning and evening light, since at these hours the
marked shadows aid materially in the suggestion of distance.

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[1] In the experiment the mask should be placed at a distance of about two meters and one
eye closed. Even with both eyes open the illusion often persists if the distance is increased to
five or six meters.

The eye, however, can aid itself in the perception of depth in ways which the painter has not at his disposal. By the sense of effort associated with the act of accommodation we are able to estimate roughly the relative distance of objects before us. This aid to our judgment can, of course, be employed only in the case of objects comparatively near the eye. Its effectiveness is greater for objects not far from the near-point of vision, and diminishes rapidly as the distance is increased, and disappears for distances more than two or three meters from the eye.

When the head is moved from side to side an apparent change in the relative position of objects at different distances is produced, and, as the extent of this change is inversely proportional to the distance of the objects, it serves as a measure of distance. This method of obtaining the "parallax" of objects by a motion of the head is often noticeable in persons whose vision in one eye is absent or defective.

Binocular Vision.—The same result which is secured by the comparison of retinal images seen successively from slightly different points of view is obtained by the comparison of the images formed simultaneously by any object in the *two eyes*. In binocular vision we obtain a much more accurate idea of the shape and distance of objects around us than is possible with monocular vision, as may be proved by trying to touch objects in our neighborhood with a crooked stick, first with both eyes open and then with one eye shut. Whenever we look at a near solid object with two eyes, the right eye sees farther round the object on the right side and the left eye farther round on the left. The mental comparison of these two slightly different images produces the perception of solidity or depth, since experience has taught us that those objects only which have depth or solidity can affect the eyes in this way. Conversely, if two drawings or photographs differing from each other in the same way that the two retinal images of a solid object differ from each other are presented, one to the right and the other to the left eye, the two images will become blended in the mind and the perception of solidity will result. Upon this fact depends the effect of the instrument known as the stereoscope, the slides of which are generally pairs of photographs of natural objects taken simultaneous-
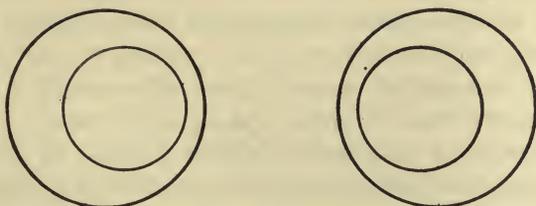
Fɪɢ. 260.—To illustrate stereoscopic vision.

ly with a double camera, of which the lenses are at a distance from each other equal to or slightly exceeding that between the two axes of vision. The principle of the stereoscope can be illustrated in a very simple manner by drawing circles such as are represented in Figure 260 on thin paper, and fastening each

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pair across the end of a piece of brass tube about one inch or more in diameter and ten inches long. Let the tubes be held one in front of each eye with the distant ends nearly in contact with each other, as shown in Figure 261. If the tubes are in such a position that the small circles are brought as near to each other as possible, as shown in Figure 260, the retinal images will blend, the smaller circle will seem to be much nearer than the larger one, and the eyes will appear to be looking down upon a truncated cone, such as is shown in Figure 262, since a solid body of this form is the only one
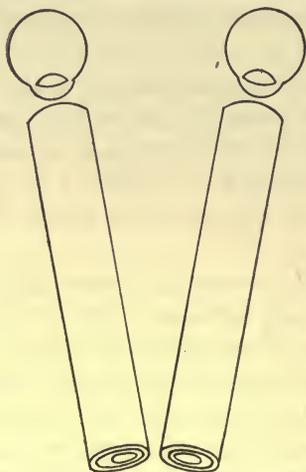
FIG. 261.—To illustrate stereoscopic vision.
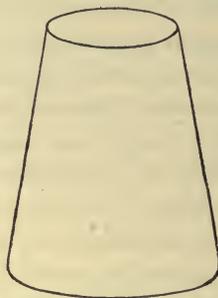
FIG. 262.—To illustrate stereoscopic vision.

bounded by circles related to each other as those shown in this experiment.

Stereoscopic slides often serve well to illustrate the superiority of binocular over monocular vision. If the slide represents an irregular mass of rocks or ice, it is often very difficult by looking at either of the pictures by itself to determine the relative distance of the various objects represented, but if the slide is placed in the stereoscope the true relation of the different parts of the picture becomes at once apparent.

Since the comparison of two slightly dissimilar images received on the two retinas is the essential condition of stereoscopic vision, it is evident that if the two pictures are identical no sensation of relief can be produced. Thus, when two pages printed from the same type or two engravings printed from the same plate are united in a stereoscope, the combined picture appears as flat as either of its components. If, however, one of the pictures is copied from the other, even if the copy be carefully executed, there will be slight differences in the distances between the lines or in the spacing of the letters which will cause apparent irregularities of level in the different portions of the combined picture. Thus, a suspected banknote may be proved to be a counterfeit if, when placed in a stereoscope by the side of a genuine note, the resulting combined picture shows certain letters lying apparently on different planes from the rest.

Pseudoscopic Vision.—If the pictures of an ordinary stereoscopic slide be reversed, so that the picture belonging in front of the right eye is presented to the left eye, and *vice versâ*, the stereoscopic gives place to what is called a pseudoscopic effect—*i. e.* we perceive not a solid but a hollow body. The effect is best

obtained with the outlines of geometrical solids, photographs of coins or medals or of objects which may readily exist in an inverted form. Where the photographs represent objects which cannot be thus inverted, such as buildings and landscapes, the pseudoscopic effect is not readily produced—another example of the power (see p. 800) of the outline of a familiar object to outweigh other sorts of testimony.

A pseudoscopic effect may be readily obtained without the use of a stereoscope by simply converging the visual axes so that the right eye looks at the left and the left eye at the right picture of a stereoscopic slide. The eyes may be aided in assuming the right degree of convergence by looking at a small object like the head of a pin held between the eyes and the slide in the manner described on p. 758. Figure 260, viewed in this way, will present the appearance of a hollow truncated cone with the base turned toward the observer. A stereoscopic slide with its pictures reversed will, of course, when viewed in this way, present not a pseudoscopic, but a true stereoscopic, appearance, as shown by Figures 226 and 227.

Binocular Combination of Colors.—The effect of binocularly combining two different colors varies with the difference in wave-length of the colors. Colors lying near each other in the spectrum will generally blend together and produce the sensation of a mixed color, such as would result from the union of colors by means of the revolving disk or by the method of reflected and transmitted light, as above described. Thus a red and a yellow disk placed in a stereoscope may be generally combined to produce the sensation of orange. If, however, the colors are complementary to each other, as blue and yellow, no such mixing occurs, but the field of vision seems to be occupied alternately by a blue and by a yellow color. This so-called " rivalry of the fields of vision " seems to depend, to a certain extent, upon the fact that in order to see the different colors with equal distinctness the eyes must be differently accommodated, for it is found that if the colors are placed at different distances from the eyes (the colors with the less refrangible rays being at the greater distance), the rivalry tends to disappear and the mixed color is more easily produced.

An interesting effect of the stereoscopic combination of a black and a white object is the production of the appearance of a metallic lustre or polish. If, for instance, the two pictures of a stereoscopic slide represent the slightly different outlines of a geometrical solid, one in black upon white ground and the other in white upon black ground, their combination in the stereoscope will produce the effect of a solid body having a smooth lustrous surface. The explanation of this effect is to be found in the fact that a polished surface reflects the light differently to the two eyes, a given point appearing brilliantly illuminated to one eye and dark to the other. Hence the stereoscopic combination of black and white is interpreted as indicating a polished surface, since it is by means of a polished surface that this effect is usually produced.

Corresponding Points.—When the visual axes of both eyes are directed to the same object two distinct images of that object are formed upon widely

separated parts of the nervous system. Yet but a single object is perceived. The phenomenon is the same as that which occurs when a grain of sand is held between the thumb and finger. In both cases we have learned (chiefly through the agency of muscular movements and the nerves of muscular sense) to interpret the double sensation as produced by a single object.

Any two points, lying one in each retina, the stimulation of which by rays of light gives rise to the sensation of light proceeding from a single object are said to be " corresponding points." Now, it is evident that the *foveæ centrales* of the two eyes must be corresponding points, for an object always appears single when both eyes are fixed upon it. That double vision results when the images are formed on points which are not corresponding may be best illustrated by looking at three pins stuck in a straight rod at distances of 35, 45, and 55 centimeters from the end. If the end of the rod is held against the nose and the eyes directed to each of the three pins in succession, it will be found that, while the pin looked at appears single, each of the others appears double, and that the three pins therefore look like five.

The two *foveæ centrales* are not, of course, the only corresponding points. In fact, it may be said that the two retinas correspond to each other, point for point, almost as if they were superposed one upon the other with the foveæ together. The exact position of the points in space which are projected on to corresponding points of the two retinas varies with the position of the eyes. The line or surface in which such points lie is known as the " horopter." A full discussion of the horopter would be out of place in this connection, but one interesting result of its study may be pointed out—viz. the demonstration that when, standing upright, we direct our eyes to the horizon the horopter is approximately a plane coinciding with the ground on which we stand. It is of course important for security in walking that all objects on the ground should appear single, and, as they are known by experience to be single, the eye has apparently learned to see them so.

Since the vertical meridians of the two eyes represent approximately rows of corresponding points, it is evident that when two lines are so situated that their images are formed each upon a vertical meridian of one of the eyes, the impression of a single vertical line will be produced, for such a line seen binocularly is the most frequent cause of this sort of retinal stimulation. This is the explanation commonly given of the singular optical illusion which is produced when lines drawn as in Figure 263 are looked at with both eyes fixed upon the point of intersection of the lines and with the plane in which the visual axes lie forming an angle of about 20° with that of the paper, the distance of the lines from the eyes being such that each line will lie approximately in the same vertical plane with one of the visual axes. Under these circumstances each line will form its image on a vertical meridian of one of the eyes, and the combination of these images results in the perception of a third line, not lying in the plane of the paper, but apparently passing through it more or less vertically, and swinging round its middle point with every movement of the head or the paper. In this experiment it will be found that the illusion

of a line placed vertically to the plane of the paper does not entirely disappear when one eye is closed. Hence it is evident that there is, as Mrs.
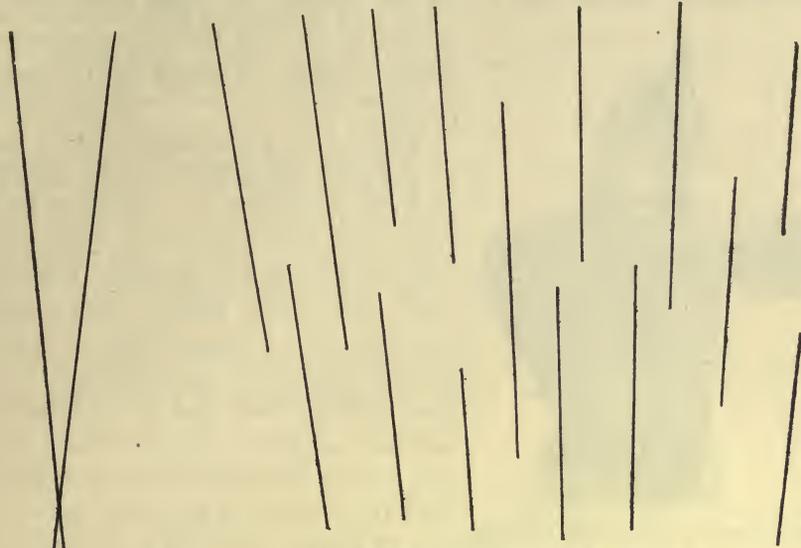
FIG. 264.—Monocular illusion of vertical lines.

FIG. 263.—Binocular illusion of a vertical line.

C. L. Franklin has pointed out,[1] a strong tendency to regard lines which form their images approximately on the vertical meridian of the eye as themselves vertical. This tendency is well shown when a number of short lines converging toward a point outside of the paper on which they are drawn, as in Figure 264, are looked at with one eye held a short distance above the point of convergence. Even when the lines are not convergent, but parallel, so that their images cannot fall upon the vertical meridian of the eye, the illusion is not entirely lost. It will be found, for instance, that when the Zöllner lines, as given in Figure 251, are looked at obliquely with one eye from one corner of the figure, the short lines which lie nearly in a plane with the visual axis appear to stand vertically to the plane of the paper.

In this connection it may be well to allude to the optical illusion in consequence of which certain portraits seem to follow the beholder with the eyes. This depends upon the fact that the face is painted looking straight out from the canvas —*i. e.* with the pupil in the middle of the eye. The painting being upon a flat surface, it is evident that, from whatever direction the picture is viewed, the pupil will always seem to be in the middle of the eye, and the eye will consequently appear to be directed upon the observer. The phenomenon is still more striking in the case of pictures of which the one represented in Figure 265 may be taken as an example. Here the soldier's rifle

[1] *Am. Journal of Psychology,* vol. i. p. 99.

is drawn as it appears to an eye looking straight down the barrel, and, as this foreshortening is the same in all positions of the observer, it is evident that when such a picture is hung upon the wall of a room the soldier will appear to be aiming directly at the head of every person present.

FIG. 265.—Illusion of lines always pointing toward observer.

In concluding this brief survey of some of the most important subjects connected with the physiology of vision it is well to utter a word of caution with regard to a danger connected with the study of the subject. This danger arises in part from the fact that in the scientific study of vision it is often necessary to use the eyes in a way quite different from that in which they are habitually employed, and more likely, therefore, to cause nervous and muscular fatigue. We have seen that in any given position of the eye distinct definition is limited to an area which bears a very small proportion to the whole field of vision. Hence in order to obtain an accurate idea of the appearance of any large object our eyes must wander rapidly over its whole surface, and we use our eyes so instinctively and unconsciously in this way that, unless our attention is specially directed to the subject, we find it difficult to believe that the power of distinct vision is limited to such a small portion of the retina. In most of the experiments in physiological optics, however, this rapid change of direction of the axis of vision must be carefully avoided, and the eye-muscles held immovable in tonic contraction.

Our eyes, moreover, like most of our organs, serve us best when we do not pay too much attention to the mechanism by which their results are brought about. In the ordinary use of the eyes we are accustomed to neglect after-images, intraocular images, and all the other imperfections of our visual apparatus, and the usefulness of our eyes depends very much upon our ability thus to neglect their defects. Now, the habit of observing and examining these defects that is involved in the scientific study of the eye is found to interfere with our ability to disregard them. A student of the physiology of vision who devotes too much attention to the study of after-images, for instance, may render his eyes so sensitive to these phenomena that they become a decided obstacle to ordinary vision.

B. The Ear and Hearing.

Anatomy and Histology of the Ear.—The organ of hearing may conveniently be divided into three parts: (1) The external ear, including the *pinna* or *auricle* and the *external auditory meatus;* (2) the middle ear, called the "tympanic cavity" or *tympanum;* and (3) the internal ear, or *labyrinth.* The labyrinth is situated in the dense petrous bone, and it contains a membranous sac of complex form which receives the peripheral terminations of the auditory nerve. This sac, therefore, is to the ear what the retina is to the eye; as the lens, cornea, etc. of the eye are simply physical media for the production of sharp images on the retina, so all parts of the organ of hearing are devoted solely to the accurate transmission of the energy of air-waves to the internal ear.

The External Ear.—*The pinna* or *auricle,* commonly known simply as the "ear" (Fig. 266), is a peculiarly wrinkled sheet of tissue, consisting essen-
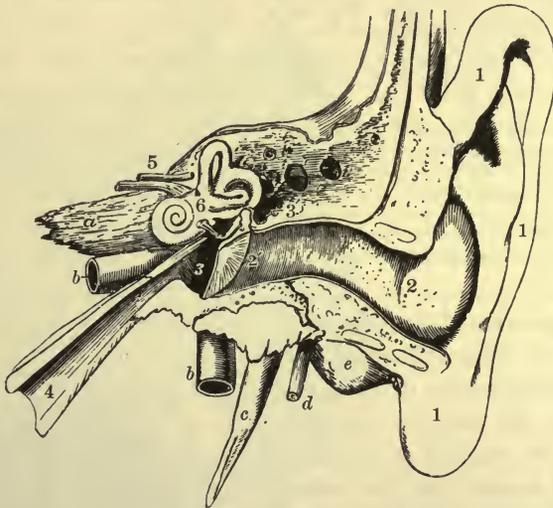
Fig. 266.—Diagram of organ of hearing of left side (Quain, after Arnold): 1, the pinna; 2, bottom of concha; 2-2′, meatus externus; 3, tympanum; above 3, the chain of ossicles; 3′, opening into the mastoid cells; 4, Eustachian tube; 5, meatus internus, containing the facial (uppermost) and auditory nerves; 6, placed on the vestibule of the labyrinth above the fenestra ovalis; *a,* apex of the petrous bone; *b,* internal carotid artery; *c,* styloid process; *d,* facial nerve, issuing from the stylo-mastoid foramen; *e,* mastoid process; *f,* squamous part of the bone.

tially of yellow elastic cartilage covered with skin, and forming at the entrance of the auditory meatus a cup-shaped depression called the "concha."

The concha, and to some extent the whole auricle, serves a useful purpose in collecting, like the mouth of a speaking-trumpet, the waves of sound falling upon it; but in many of the lower animals the concha is relatively larger than in man, and, their ears being freely movable, the auricle becomes of greater physiological importance.

External Auditory Meatus.—In man the *external auditory meatus* or auditory canal is about one and a quarter inches in length, and it extends from

the bottom and anterior edge of the concha to the *membrana tympani,* or

tympanic membrane. Starting from the bottom of the concha, the general direction of the auditory canal is first obliquely upward and backward for about half an inch, and then inward and forward. Therefore, to look into the ear or to introduce the aural speculum the canal must be straightened by pulling the pinna upward and backward. The canal-wall is cartilaginous and movable for about half an inch from the exterior, but is osseous for the rest of its extent; it is lined by a reflexion of thin skin, on whose surface, in the cartilaginous part of the canal, open the ducts of numerous sebaceous and ceruminous glands.

FIG. 267.—Tympanum of left ear, with ossicles *in situ* (after Morris): 1, suspensory ligament of malleus; 2, head of malleus; 3, epitympanic region; 4, external ligament of malleus; 5, processus longus of incus; 6, base of stapes; 7, processus brevis of malleus; 8, head of stapes; 9, *os orbiculare;* 10, manubrium; 11, Eustachian tube; 12, external auditory meatus; 13, *membrana tympani;* 14, lower part of tympanum.

Tympanum.—The middle ear, or *tympanum* (Figs. 266, 267), is shut off from the auditory canal by the tympanic membrane. It is an air-holding cavity of irregular shape in the petrous bone, and it is broader behind and above than it is below and in front. Posteriorly it is in open communication with the complex system of air-cavities in the mastoid bone known as the *mastoid antrum* and the *mastoid cells.* Anteriorly it is continuous with the pharynx through the Eustachian tube. The inner wall slants somewhat outward from top to bottom, and it is formed chiefly by part of the bony envelope of the internal ear. The surface of this wall is pierced by two apertures, the *fenestra ovalis,* or oval window, and the *fenestra rotunda,* or round window, leading into the cavity of the bony labyrinth; in life each fenestra is covered by a thin sheet of membrane, and the foot of the *stapes* is fastened by a ligamentous fringe in the

FIG. 268.—Otoscopic view of left *membrana tympani* (Morris): 1, *membrana flaccida;* 2, 2', folds bounding the former; 3, reflection from processus brevis of malleus; 4, processus longus of incus (occasionally seen); 5, membrana tympani; 6, *umbo* and end of manubrium; 7, pyramid of light.

oval window. The outer wall of the middle ear is made up of the tympanic

membrane and the ring of bone into which this membrane is inserted. The roof is formed by a thin plate of bone, the *tegmen*, which separates it from the cranial cavity, and the narrow floor, concave upward, is just above the jugular fossa. The cavity is lined by mucous membrane continuous with that of the Eustachian tube and the pharynx, and the membrane, like that of the Eustachian tube, is ciliated except over the surfaces of the ossicles and the tympanic membrane. Suppurative inflammation of the middle ear may not only involve the mastoid cells, but may also cause absorption of the thin plate of bone forming the roof of the tympanic cavity and the mastoid antrum. In this and in other ways inflammation may extend from the tympanic to the cranial cavity, making *otitis media*, or inflammation of the middle ear, the commonest source of pyogenic affections of the brain.[1]

Tympanic Membrane, or Drum-skin.—The membrana tympani (Figs. 268, 269) is a somewhat oval disk whose longer axis is directed from behind and above

downward and forward, and whose length is about nine millimeters. The membrane is inserted obliquely to the axis of the auditory canal, so that the floor of the canal is longer than its roof. The membrana tympani, though so thin as to be semi-transparent, is composed of three layers of tissue. Externally it is covered by a thin plate of skin; internally, by mucous membrane; and between these lies the proper sub-

Fig. 269[2].—Tympanum of right side with ossicles in place, viewed from within (after Morris): 1, body of incus; 2, suspensory ligament of malleus; 3, ligament of incus; 4, head of malleus; 5, epitympanic cavity; 6, *chorda tympani* nerve; 7, tendon of *tensor tympani* muscle; 8, foot-piece of stirrup; 9, *os orbiculare*; 10, manubrium; 11, tensor tympani muscle; 12, membrana tympani; 13, Eustachian tube.

Fig. 270.—The chain of auditory ossicles, anterior view (after Testut): 1, head of malleus; 2, long process of incus; 3, stapes.

stance (*membrana propria*) of the membrane, made up chiefly of fibrous tissue. The greater number of the fibres of the membrana propria radiate from near the centre to the periphery of the membrane; but there are also circular fibres of elastic tissue which are most numerous in a ring near the attached margin of the membrane. The surface of the tympanic membrane is not flat, but is funnel-shaped, with the apex of the funnel pointing inward. Moreover, lines

[1] Macewen: *Pyogenic Diseases of the Brain and Spinal Cord*, 1893.

[2] Figs. 267, 268, and 269 are taken by permission from Morris's *Text-Book of Anatomy*, Phila., 1893.

drawn from the centre to the margin of the membrane would not be straight, but would be curved slightly, with the convexity outward, this shape being due to the tension of the elastic circular fibres of the membrane. The membrane, throughout the greater part of its circumference, is inserted in a groove in a bony ring set in the wall of the auditory canal, but a small arc at its superior portion is attached directly to the wall of the canal. The segment of membrane corresponding to this arc, known as the *membrana flaccida,* lacks the tenseness of the rest of the drum-skin.

Viewed through the aural speculum, the normal tympanic membrane has a pearly lustre (Fig. 268). The handle of the malleus, or *manubrium,* inserted within its fibrous layer, can be seen as an opaque ridge running from near the upper anterior margin downward and backward and ending in the *umbo,* or central depression, where the membrane is drawn considerably inward by the tip of the manubrium. It is from this point that the radial fibres of the *membrana propria* diverge.

At the top of the manubrium is a shining spot which is the reflection from the short process of the malleus where it presses against the membrane. From this point two delicate folds of the membrane run to the periphery— one forward and the other backward. They form the lower border of the *membrana flaccida,* or *Shrapnell's membrane,* in which there is less fibrous tissue than in the remaining part of the membrane, and the cutaneous and mucous layers are also less tense than elsewhere. A bright reflection of triangular shape, known as the "pyramid of light," is seen in the lower quadrant of the tympanic membrane. The apex of this bright triangle is at the tip of the manubrium, and its base is on or near the periphery of the membrane.

FIG. 271.—Malleus of the right side : A, anterior face ; B, internal face (after Testut) : 1, capitulum or head of malleus ; 2, cervix or neck ; 3, processus brevis ; 4, processus gracilis ; 5, manubrium ; 6, grooved articular surface for incus ; 7, tendon of m. tensor tympani.

Auditory Ossicles. — The tympanic membrane is put into relation with the internal ear by a chain of bone, the *auditory ossicles,* known as the *malleus,* the *incus,* and the *stapes,* so called from their fancied resemblance to a hammer, an anvil, and a stirrup (Figs. 267, 269, 270). The malleus (Fig. 271) is 18 to 19 millimeters long ; it presents a rounded head, grooved on one side for articulation with the incus, a short neck, and a long handle or *manubrium,* which is inserted in the tissue of the tympanic membrane from a point on its upper periphery to a little below its centre. The *processus brevis* of the malleus is a low conical projection which springs from the top of the manubrium and presses directly against that segment of the tympanic membrane known as the *membrana flaccida,* through which it can be seen shining on inspection with the ear-speculum. The *processus gracilis,* or *pro-*

cessus Folianus, long and slender, arises from an eminence just below the neck of the malleus, and, passing forward and outward, is inserted in the Glaserian fissure in the wall of the tympanum. The malleus is held in position partly by ligaments; the *suspensory* or *superior ligament* passes downward and outward from the roof of the tympanum to be inserted into the head of the malleus. The main portion of the *anterior ligament* is attached to the neck of the malleus just above the *processus gracilis;* it embraces the latter, and, passing forward, finds its origin in the anterior wall of the tympanum and in the Glaserian fissure. Another division of this ligament, the *external ligament,* arises and is attached more externally than that just described. The ligaments of the malleus serve to keep its head in position. The external ligament, being attached above the axis of rotation of the hammer, prevents the head of this bone from moving too far inward, and the manu-

FIG. 272.—Ligaments of the ossicles and their axis of rotation (from Foster, after Hensen). The figure represents a nearly horizontal section of the tympanum, carried through the heads of the malleus and incus: *M,* malleus; *I,* incus; *t,* articular tooth of incus; *lg.a* and *lg.e,* external ligament of malleus; *lg.inc,* ligament of the incus; the line *a–x* represents the axis of rotation of the two ossicles.

brium from being pushed too far outward. The superior ligament, owing to its oblique course, restrains the head of the hammer from moving too far outward.

The *incus, ambos,* or anvil-bone (Fig. 273) is shaped somewhat like a bicuspid tooth. Its thicker portion is hollowed on the surface and is covered with cartilage for articulation with the head of the malleus. It has two processes, a long and a short, which project at right angles to
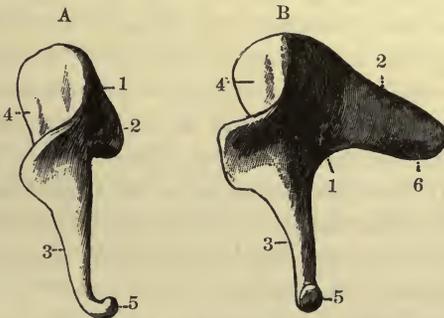
FIG. 273.—The incus of the right side: A, anterior face; B, internal face (after Testut): 1, body of incus; 2, processus brevis; 3, processus longus; 4, articular surface for the malleus; 5, a convex tubercle, processus lenticularis, for articulation with stapes; 6, rough surface for attachment of the ligament of the incus.

FIG. 274.—The stapes (after Testut): 1, base; 2, anterior crus; 3, posterior crus; 4, articulating surface of head of the bone; 5, cervix or neck.

each other; the former has a length of $4\frac{1}{2}$ millimeters, and the latter a length of 3 to $3\frac{1}{2}$ millimeters. When in position the long process descends nearly parallel with the manubrium, but it has less than three-fourths the length of the latter. The free end of the long process is turned sharply inward at right angles, and terminates in a round projection, the *os orbiculare,* which is provided with cartilage for articulation with the head of the *stapes.* The short process is

conical in shape and is thicker than the long process. It has a horizontal position, and is attached by a thick ligament to the posterior wall of the tympanum.

The *stapes* (Fig. 274) articulates with the end of the long process of the incus; its plane is horizontal and about at right angles to that process. It measures 3 to 4 millimeters in length and about $2\frac{1}{2}$ millimeters in breadth. The base of the stapes is somewhat oval in shape, the superior margin being convex and the inferior being slightly concave. It is set in the fenestra ovalis, an aperture measuring about 3 millimeters by $1\frac{1}{2}$ millimeters, and is held in place by a narrow membrane made up of radial fibres of connective tissue. When in position, the inner face of the base of the stirrup is covered with lymphatic endothelium and is washed by the perilymph of the internal ear; the outer face, like the other tympanic bones and the wall of the cavity, is covered by thin mucous membrane.

Movement of the Ossicles.—The malleus-incus articulation is so arranged that with outward movements of the manubrium the head of the malleus glides freely in the joint; but the lower margins of the articulating surfaces project in such a way that the prominences lock together when the manubrium moves inward. Thus, in inward movements of the tympanic membrane and its attached manubrium, the malleus and the incus move together like one rigid piece of bone, the motions of the manubrium and the long process of the incus being parallel. Of the malleus-incus articulation Helmholtz[1] says: " In its action it may be compared with the joints of the well-known Breguet watch-keys, which have rows of interlocking teeth, offering scarcely any resistance to revolution in one direction, but allowing no revolution whatever in the other." In the outward movements the locking teeth or projections are probably still kept in apposition, under ordinary circumstances, through the elastic reaction of the ligament and the stapedial attachment of the incus. Should, however, the tympanic membrane be forced unduly outward, as by increase of pressure within the tympanum or by rarefaction of air in the auditory meatus, the incus only follows the malleus for a certain distance, the latter completing its motion by gliding in the joint. There is thus no danger of the stapes being torn out of the oval window. The hammer and the anvil, suspended by their ligaments, move freely about an axis one end of which is found at the origin of the anterior part of the anterior ligament of the malleus, and the other end in the origin of the ligament which is continuous with the short process of the incus (Fig. 272). In inward motions of the tympanic membrane the ossicles move like a single bone around the axis of suspension; and as the distance measured from the axis of rotation to the tip of the manubrium, where the power is applied, is about one and one-half times the distance to the end of the long process of the incus, where the effect is produced, the motions transmitted to the stapes can have but two-thirds the amplitude of the movements of the tip of the manubrium, but have one and one-half times their force. It will be noticed that a large proportion of the mass of both anvil and hammer is found above their axis of rotation; this upper portion acts as a counterpoise to the parts below which are directly

[1] *Sensations of Tone*, trans. by Ellis, 1885, p. 133.

concerned in the lever action. The bony lever being thus balanced, it is less difficult to understand its known sensitiveness to impulses that are inconceivably weak. The tense tympanic membrane, by reason of its funnel shape, resists strong inward compression ; hence the stapes is prevented from being pressed too far inward. The maximum amplitude of motion of the stapes in the fenestra is very small, being only about $\frac{1}{18}$ millimeter to $\frac{1}{14}$ millimeter, while that of the centre of the tympanic membrane is about $\frac{1}{12}$ millimeter to $\frac{1}{9}$ millimeter.

The functional movements of the auditory ossicles are not molecular but are molar vibrations, the chain of bones moving in a body. The sole purpose of this apparatus of the middle ear is to transmit exactly the variations of pressure in the air of the external auditory meatus to the perilymph which bathes the foot of the stapes—in other words, to convert air-waves into a similar series of water-waves. In the words of Helmholtz,[1] "The mechanical problem which the apparatus within the drum of the ear had to solve was to transform a motion of great amplitude and little force, such as impinges on the drum-skin, into a motion of small amplitude and great force, such as had to be communicated to the fluid in the labyrinth."

The adaptation of the apparatus of the middle ear to this end is worthy of careful consideration. In the first place, it will be noticed that the area of the fenestra ovalis which receives the impulses of the stapes is but a small fraction of the surface of the tympanic membrane on which the air-waves impinge, the latter area being some fifteen to twenty times greater than the former, so that the energy of air-motion is, in a fashion, concentrated. In the second place, as previously observed, the lever mechanism of the auditory ossicles is such that the movements of the end of the long process of the incus have two-thirds the amplitude of those of the tip of the manubrium, but about one and one-half times their force. It should also be noticed that the membrane fastening the foot of the stapes in the fenestra is somewhat less tense on the upper side, so that the top of the oval foot-piece has a freer motion than the bottom, and the head of the stirrup rises slightly with inward motions. In the third place, it has been demonstrated by Helmholtz[2] that the shape of the tympanic membrane peculiarly adapts it for transforming weak movements of wide amplitude into strong ones of small compass. For this membrane is not a simple funnel depressed inwardly, but the radii are slightly curved with the convexity outward, a shape chiefly due to the tension of the elastic circular fibres of the membrane on its inner face, these being most numerous toward the circumference. Air-waves beating upon this convexity flatten the curve somewhat, and their whole energy must be concentrated, with increased intensity but loss of motion, at the central point of the membrane. This effect may be illustrated by holding a slightly-curved brass wire, several inches in length, with its plane perpendicular to the surface of a table and supported on its ends. When one end of the wire is held immovable, up-and-down motions of the arch are transferred to the free end with diminished

[1] *Op. cit.*, p. 134.   [2] *Op. cit.*

amplitude. The wire represents a single radial fibre of the tympanic membrane, and the funnel shape of this membrane is adapted to concentrating this motion of the radial fibres upon the manubrium. The same effect is illustrated by the fact that when a string or a rope is stretched between two points, no matter how tightly, it always sags at its middle; the weight of the cord, however slight, is sufficient to give it a curved course, and produces a corresponding traction on the points of support.

Eustachian Tube.—That the tympanic membrane may maintain its freedom of motion, it is obviously necessary that the *average* atmospheric pressure on each side of it should remain the same. This equality of pressure is maintained through the medium of the *Eustachian tube*, a somewhat trumpet-shaped canal which, beginning in the lower anterior walls of the tympanum, runs downward, forward, and inward, and terminates in a slit in the side of the upper part of the pharynx. The Eustachian tube is lined, like the walls of the tympanum, with ciliated epithelium, the cilia working in such a way as to carry into the pharynx such secretions as may arise from the mucous membrane of the middle ear. The pharyngeal opening of the Eustachian tube is probably normally closed, but it may easily be made to open by increase or decrease of air-pressure within the pharynx, as may be produced by closing the nose and mouth and either forcing air into the pharynx by strong expiration or rarefying it by suction. In the former case the air-pressure within the tympanum is increased, and in the latter it is diminished. When air is thus made to enter or to leave the tympanum, a sensation of a sudden snap and a dull crackling noise in the ear is experienced. The lower end of the tube is normally opened during the act of swallowing, and it is at this moment that the intra- and extra-tympanic air-pressures are equalized.

Muscles of the Middle Ear.—Two muscles are devoted to adjusting the tension of the auditory mechanism of the middle ear. The *tensor tympani* is lodged within a groove which is just above and about parallel with the Eustachian tube. It terminates externally in a long tendon which bends nearly at right angles round the outer edge of the groove and is inserted into the handle of the malleus near the neck. Contraction of the tensor tympani thus results in pulling the tympanic membrane inward and rendering it more tense (Pl. 2, Fig. 1). This increase of tension of the membrane seems to adapt it better to the more rapid vibrations of high musical notes, but allows less ready response to lower notes. It is said that the tensor tympani comes normally into action at the beginning of a sound, thus tuning the membrane for the note that is to follow, and then relaxes. One of its effects is probably to bring closely together the toothed processes of malleus and incus at the beginning of a sound, so that there shall be no loss of motion during the vibrations of the membrane. The *stapedius* is a small muscle imbedded in the inner wall of the tympanum near the fenestra ovalis. Its tendon, passing forward, is inserted into the neck of the stapes. Contraction of the muscle would cause a slight rotation of the stapes round a vertical axis, so that the hinder part of the foot of the ossicle would be pressed more deeply into the fenestra, while

the remaining portion would be drawn out of it. Its action probably reduces the pressure in the cavity of the perilymph, and thus is antagonistic to that of the tensor tympani (Pl. 2, Fig. 2, A, B).

Vibrations of the Tympanic Membrane.—It is a general physical law that every elastic body can be made to vibrate more easily at one definite rate than at any other. The musical tone represented by this rate of vibration is known as the *prime* or fundamental tone of the body. Membranes have fundamental tones (see p. 827), whose pitch is determined by their area, thickness, and tension, but they differ from rods and strings in being less strictly confined to a single fundamental tone in their vibration. The tympanic membrane is quite peculiar in that it can hardly be said to have a definite fundamental tone. It would obviously be a great imperfection in an organ of hearing were certain sounds intensified by it out of proportion to others, as would be the case if the tympanic membrane had a marked fundamental tone of its own. This is prevented in the case of the membrana tympani probably both by reason of the peculiar form of its surface and its structure, and also because its oscillations are damped by the pressure of the malleus held in position by the other mechanisms of the tympanum. When the tympanic membrane is perforated or is wholly removed, without destructive inflammatory changes in the middle ear, sounds are still heard, though usually with diminished loudness. A musician who had suffered this accident was no longer able to play his violin, probably because sounds of different pitch ceased to be perceived in their true relations of loudness. We may thus conclude that the function of the tympanic membrane is not only to guard against injury to the delicate membranes of the fenestræ and the internal ear, but also to transmit to the ossicles sonorous vibrations with their true proportion of intensity. The membranes covering the round and oval windows of the internal ear have no means of damping sympathetic vibrations (see p. 829), and, should complex air-waves strike directly upon them, they would, probably, by sympathetic resonance, respond more powerfully to tones of certain pitch than to any others.

The sensation of sound may be excited by conduction through the bones of the skull as well as in the ordinary way. Thus, a tuning-fork set vibrating and held between the teeth or on the forehead is heard perfectly, and more loudly when the ears are closed than when open. The vibrations thus conducted probably partly affect the internal ear directly, and partly indirectly by setting in oscillation the tympanic membrane. When a sounding tuning-fork is held between the teeth until the sound dies away, it may still be heard if held in front of the ear, though the contrary statement is frequently erroneously made. When the sound of the fork held between the teeth has failed, it may again be heard by stopping the ears.

The Internal Ear, or Labyrinth.—The internal ear is the site of the true organ of hearing. The *membranous labyrinth* (Pl. 2, Fig. 4; Fig. 278) is a complicated system of membranous tubes and sacs, in which terminate at particular points the filaments of the auditory nerve; it is contained within a chamber, the bony labyrinth, hollowed out in the petrous bone. The cavity of the bony

labyrinth (Figs. 275, 276) consists of a median part, the *vestibule*, which is pro-
longed posteriorly in the system of *semicircular canals* and anteriorly in the
cochlea. The vestibule is a space which measures about one-fifth of an inch
in diameter, and it is perforated in its outer wall by an oval opening known
as the *fenestra ovalis*. The *semicircular canals* are three tubes of circular
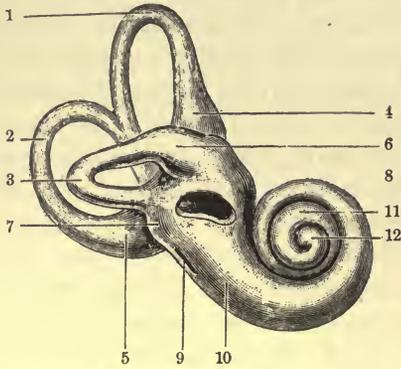
FIG. 275.—Right bony labyrinth, viewed from
outer side: the figure represents the appearance
produced by removing the petrous bone down to
the denser layer immediately surrounding the
labyrinth (from Quain, after Sömmering): 1, 2, 3,
the superior, posterior, and horizontal semicir-
cular canals; 4, 5, 6, the ampullæ of the same;
7, the vestibule; 8, the fenestra ovalis; 9, fenestra
rotunda; 10, first turn of the cochlea; 11, second
turn; 12, apex.
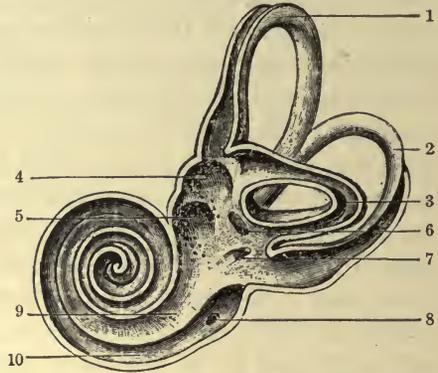
FIG. 276.—Interior view of left bony labyrinth after
removal of the superior and external walls (from
Quain, after Sömmering): 1, 2, 3, the superior, pos-
terior, and horizontal semicircular canals; 4, fovea
hemi-elliptica; 5, fovea hemispherica; 6, common
opening of the superior and posterior semicircular
canals; 7, opening of the aqueduct of the vestibule;
8, opening of the aqueduct of the cochlea; 9, the
scala vestibuli; 10, scala tympani; the lamina spiralis
separating 9 and 10.

section, known respectively as the anterior or superior, the posterior, and the
external or horizontal semicircular canal. Their planes are at right angles to
one another, so that they occupy the three possible dimensions of space. The
external canal lies in a nearly horizontal plane, while the other two approach
the vertical. Each canal is dilated at one extremity into a globular cavity
which is more than twice the diameter of the
canal itself, and which is known as the *am-
pulla*. The anterior and posterior canals
unite near the ends not provided with am-
pullæ, and they enter the vestibule as a com-
mon tube. Anteriorly the cavity of the
vestibule is continued as a tube of complex
internal structure which is coiled upon itself
two and one-half times, and which, from its
resemblance to the shell of a snail, is known
as the *cochlea* (Pl. 2, Fig. 3). The osseous
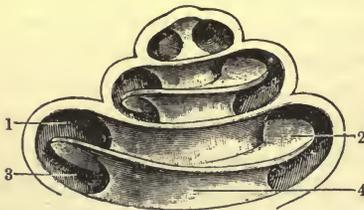
FIG. 277.—Diagram of the osseous cochlea
laid open (after Quain): 1, scala vestibuli;
2, lamina spiralis; 3, scala tympani; 4, cen-
tral pillar or modiolus.

cochlea may be conceived as formed by a bony tube turned about a bony central
pillar, the *modiolus*, which diminishes in diameter from the base to the apex
of the cochlea. From the modiolus a bony shelf stretches into the cavity of
the tube, incompletely dividing it into two tubular chambers, winding round
the modiolus like a circular staircase, the upper of which chambers we shall

Explanation of Plate 2.

Fig. 1.—Schematic representation of displacement of the auditory ossicles due to contraction of the tensor tympani muscle (Testut): *a*, external auditory meatus; *b*, tympanic cavity; *c*, vestibule of the bony labyrinth; *d*, fenestra ovalis; 1, membrana tympani; 2, handle of malleus; 3, head of malleus; 4, insertion of tendon of tensor tympani; 5, long or vertical process of incus; 6, head of incus; 7, stapes. (The arrow indicates the direction of traction of the tensor tympani muscle; and the lines in red indicate the change in the position of the parts produced by it.)

Fig. 2.—Schematic representation of the displacement of the stapes due to contraction of the stapedius muscle (Testut): *A*, the stapes in repose; *B*, stapes during contraction of stapedius muscle; 1, base of stapes; 2, anterior border of fenestra ovalis; 3, the pyramid; 4, tendon of stapedius muscle; *a*, anterior portion of annular ligament of stapes, longer than *b*, posterior portion of same ligament; *x, x*, anteroposterior diameter of fenestra ovalis, passing through the base of the resting stapes; *y*, point of passage of the vertical line which represents the axis of rotation of the stapes.

Fig. 3.—The three parts making up the bony cochlea (schematic, from Testut): *A*, the columella; *B*, spiral tube containing the scalæ; *C*, lamina spiralis; *D*, the three parts in their normal relations.

Fig. 4.—Schematic representation of the perilymphatic and endolymphatic spaces. The former appear in black, and the latter are colored blue (Testut): 1, utricle; 2, saccule; 3, semicircular canal; 4, canalis cochlearis; 5, ductus endolymphaticus with its two branches of origin; 6, saccus endolymphaticus; 7, canalis reuniens, or canal of Hensen; 8, scala tympani; 9, scala vestibuli; 10, their communication at the helicotrema; 11, aquæductus vestibuli; 12, aquæductus cochlearis; 13, periosteum; 14, dura mater; 15, stapes in the fenestra ovalis; 16, fenestra rotunda with its membrane.

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.
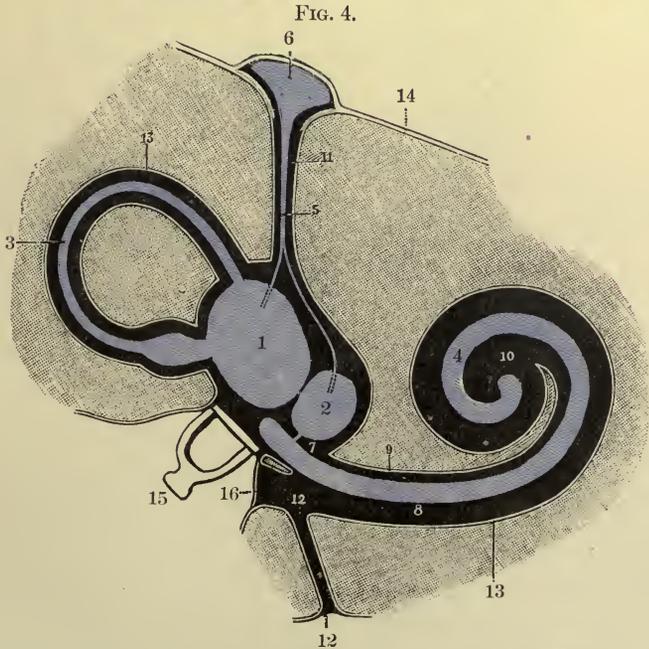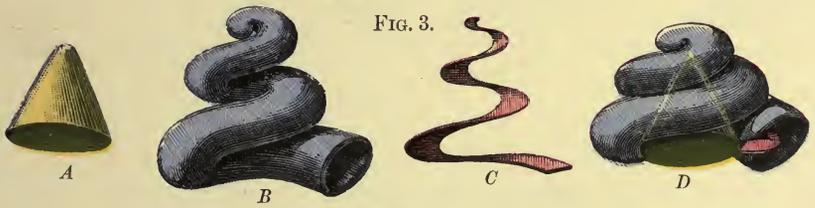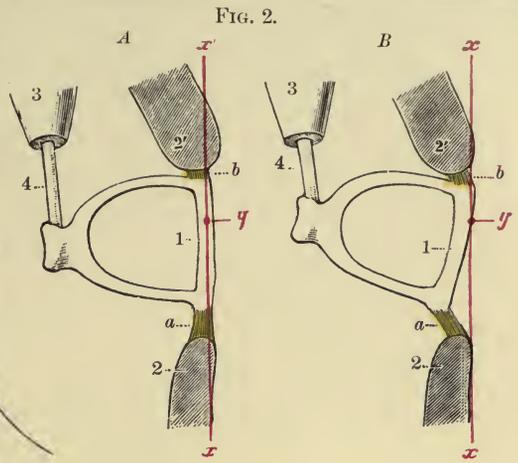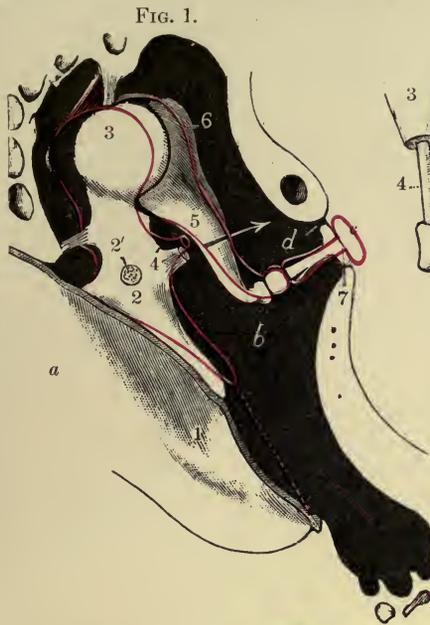
soon learn to know as the *scala vestibuli,* and the lower chamber as the *scala tympani* (Fig. 277; Pl. 2, Fig. 3). The bony shelf mentioned above as partly bisecting the cochlear tube has, of course, like the latter, a spiral course, and is known as the *lamina spiralis;* its importance as a supporter of the auditory-nerve filaments will soon be seen.

Contained within the cavity of the bony labyrinth, and parallel with its walls, is the *membranous labyrinth,* in which are found the essential structures of the organ of hearing (Pl. 2, Fig. 4; Fig. 278). The membranous labyrinth is filled with a somewhat watery, mucin-holding fluid, the *endolymph,* while a similar fluid, the *perilymph,* is found outside it and within the osseous labyrinth. The perilymph space, which is lined by lymphatic epithelium, is in communication, along the sheath of the auditory nerve, with the subdural and subarachnoid lymph-areas of the brain. Numerous sheets and bars of connective tissue cross from the wall of the bony to that of the membranous labyrinth and help support the latter. That part of the membranous labyrinth lying within the vestibule is composed of two separate sacs—a larger posterior, known as the *utricle* or *utriculus,* and a smaller, more anterior, known as the *saccule* or *sacculus.* The plane of division between the two sacs ends opposite the fenestra ovalis (Pl. 2, Fig. 4). Though the sacs are quite separate, their cavities are indirectly continu-
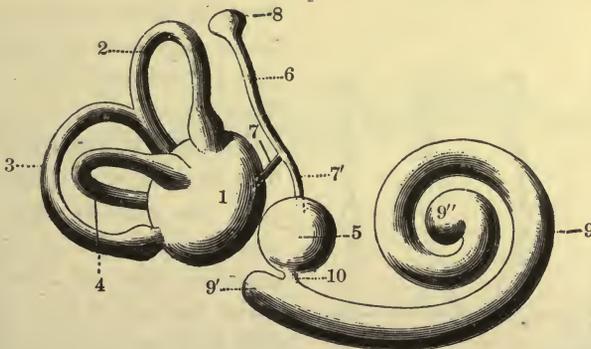
Fig. 278.—Diagram of right membranous labyrinth seen from the external side (after Testut): 1, utricle; 2, 3, 4, superior, posterior, and horizontal semicircular canals; 5, saccule; 6, ductus endolymphaticus, with 7, 7', its twigs of origin; 8, saccus endolymphaticus; 9, canalis cochlearis, with 9', its vestibular cul-de-sac, and 9'', its blind extremity; 10, canalis reuniens.

ous, through the union of two small tubes arising from either sac, which tubes unite to form the *ductus endolymphaticus,* a tube running inward through a canal in the petrosal bone and ending blindly in a dilated flattened extremity, the *saccus endolymphaticus,* this being supported between the layers of the *dura mater* within the cavity of the skull (Pl. 2, Fig. 4). Bundles of auditory-nerve fibres penetrate the wall of each sac. The utricle gives rise to the membranous semicircular canals, which communicate with it at five points, it being remembered that the anterior and posterior canals fuse into a single tube at the ends not provided with ampullæ, and that they have a common entrance into the utricle. The saccule is continuous by a narrow tube, the *canalis reuniens,* with that division of the membranous labyrinth contained

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within the cochlea and known as the *canalis cochlearis.* The auditory nerve really consists of two distinct divisions having separate origins and different distributions. One of these branches passes finally to the cochlea, and the other to the vestibule and the semicircular canals. The nerve approaches the labyrinth by way of a canal known as the *meatus auditorius internus,* and on reaching the angle between the vestibule and the base of the cochlea the cochlear division passes to the cochlea. The remainder of the nerve consists of two divisions, the superior of which is distributed to the utricle and to the ampullæ of the anterior and horizontal semicircular canals; the inferior branch supplies the saccule and the posterior semicircular canal. The inner wall of both utricle and saccule is developed at a particular spot into a low mound, the *macula acustica,* made up of an accumulation of the connective-tissue elements of the membranous wall and covered by a peculiarly modified epithelium, the *auditory epithelium* (Fig. 279). All the auditory-nerve filaments that enter the saccule and utricle respectively pass to these mounds and there enter into relation with the auditory epithelium.

As the auditory-nerve endings are confined to a particular area in the utricle and the saccule, so the nerve-fibres supplying the semicircular canals are limited to a certain part of the ampulla of each canal. The tissue of the wall of the ampulla is developed into a ridge projecting into the cavity in a direction across its long axis. This ridge, present in each ampulla, is called the *crista acustica ;* it is capped by a thick layer of columnar epithelial cells, the auditory epithelium, which thins away at the border of the crista into the sheet of flattened cells by which the rest of the ampulla is lined. The auditory cells (Fig. 279) are said to be of two kinds—one, cylindrical in shape and reaching only part way to the basement membrane, the *hair-cells ;* the other, narrow and elongated, the supporting or *sustentacular cells.* The former are peculiar in the fact that from their free ends there project long, stiff, hair-like processes. The filaments of the ampullary-nerve branches pass through the cristæ and encircle the bodies of the hair-cells. The cells covering the *maculæ acusticæ* have essentially the same structure as those just described, though in the maculæ the auditory hairs are shorter than in the cristæ. Seated on the free surface of the macular epithelium is a fibrous mass which is said to be a normal structure, and not, like a somewhat similar mass found covering the cristæ in post-mortem sections, a coagulum due to the method of preparation. Imbedded in the membrane over the maculæ of both saccule and utricle are

Fig. 279.—Diagram showing the epithelial cells of a macula or a crista (after Foster): 1, cylinder or hair-cell; 2, the same, enveloped in a nest of nerve-fibrils; 3, 4, 5, forms of rod- or spindle-cells.

small crystals, *otoliths* or *otoconia*, composed chiefly of carbonate of lime. Otoconia are also found less constantly in the ampullæ and even in the perilymph space of the cochlea. In fishes there are large masses of calcareous matter, otoliths, attached to the wall of the auditory sac.

General Anatomy of the Cochlea.—By far the most complex structure of the ear is found in the cochlea (Pl. 2, Figs. 1, 3, 4; Figs. 275–278). The bony cochlea continues from the anterior wall of the vestibule, and in the upright position of the head the axis of the modiolus is nearly horizontal, pointing, from base
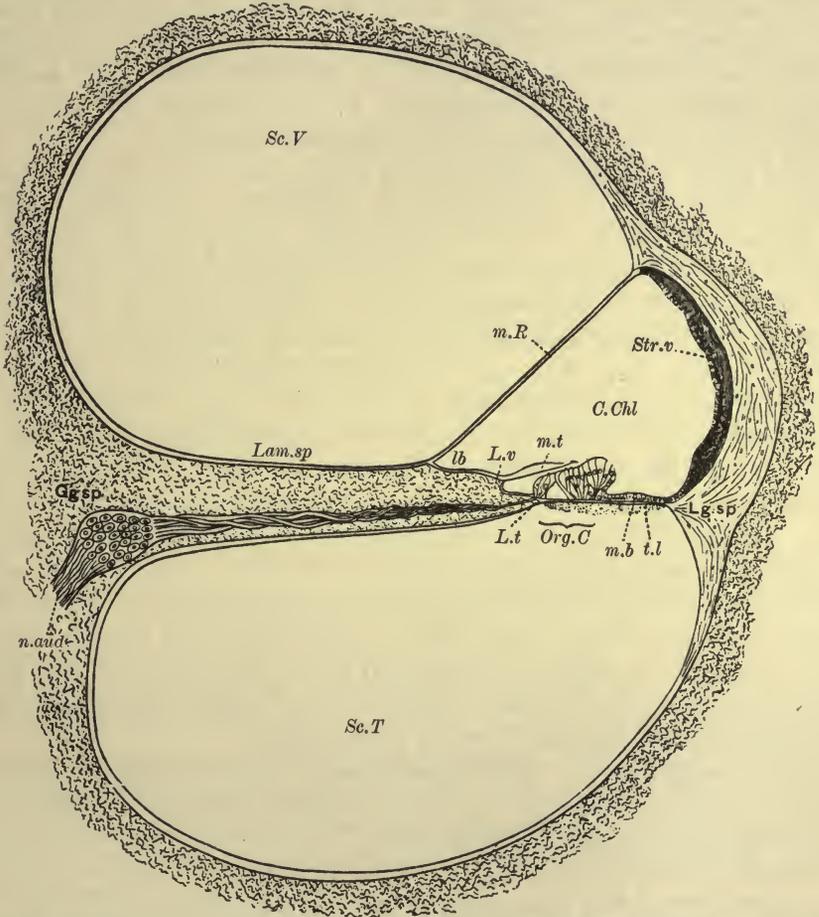
Fig. 280.—Diagram of a transverse section of a whorl of the cochlea (after Foster): *Sc.V*, scala vestibuli; *Sc.T*, scala tympani; *C.Chl*, canalis cochlearis; *Lam.sp*, lamina spiralis; *Gg.sp*, ganglion spirale; *n.aud*, auditory nerve; *m.R*, membrane of Reissner; *Str.v*, stria vascularis; *Lg.sp*, ligamentum spirale; *t.l*, lymphatic epithelioid lining of basilar membrane on the tympanic side; *m.b*, basilar membrane; *Org.C*, organ of Corti; *L.t*, labium tympanicum; *lb*, limbus; *L.v*, labium vestibulare; *m.t*, tectorial membrane.

to apex, outward and slightly down and forward, the base of the cochlea being formed by the inner surface of the petrous bone. The membranous cochlea, *canalis* or *ductus cochlearis*, is a tube of nearly triangular cross-section which winds round the modiolus from base to apex (Fig. 280). The base or outer side

of this triangle is attached closely to the bony wall of the cochlea; the upper side, supposing the modiolus to be vertical with its apex above, is made of a thin sheet of cells known as the *membrane of Reissner;* the lower side is made up partly of the bony margin of the *lamina spiralis* and partly of a membrane, radially striated, stretched across from the edge of the spiral lamina to the side wall of the cochlea; this is called the basilar membrane, *membrana basilaris.* The coiled tube forming the bony cochlea is thus divided by the *lamina spiralis* and the *canalis cochlearis* into three tubes which wind spirally and parallel round the modiolus. The *canalis cochlearis* contains endolymph, and its cavity ends blindly above and below, but is continuous by way of the narrow *canalis reuniens* with that of the saccule. The tubes above and below the *canalis cochlearis* are perilymph-spaces; it will be noticed that there is no such space on the outer side of the membranous cochlea.

The upper tube, when followed down to the base of the cochlea, is found to open freely into the vestibule of the labyrinth; it is therefore known as the *scala vestibuli.* The lower tube ends blindly at the base of the cochlea, but, where this part bulges into the tympanum as the "promontory" of its inner wall, it is perforated by the aperture known as the *fenestra rotunda,* whose proper membrane alone prevents the perilymph from escaping into the middle ear. This tube is therefore known as the *scala tympani.* From its central position the membranous cochlear canal is frequently known as the *scala media.* The scala vestibuli and the scala tympani both decrease in size as they wind from the base to the apex or *cupola* of the cochlea; the membranous cochlear canal, on the contrary, increases in section from base to apex until near the top; hence the width of the basilar membrane and the length of its radial fibres increase from below upward. The scala vestibuli and the scala tympani have no communication except through a small aperture under the cupola of the cochlea, known as the *helicotrema;* this is bounded by the hook-like termination, the *hamulus,* of the bony lamina spiralis, which forms the greater part of a ring completed by the pointed blind extremity of the canalis cochlearis fastened above it to the cupola.

The Transmission of Vibrations through the Labyrinth.—Vibrations of the tympanic membrane are transmitted as pulses of very small amplitude to the membrane covering the fenestra ovalis. The relatively considerable body of perilymph bathing the inner face of this membrane must be thus set in motion, and there starts a fluid-wave which is free to make its way throughout the perilymph-spaces of the vestibule and the semicircular canals. It may pass from the vestibule along the scala vestibuli to its top, through the helicotrema, and back by way of the scala tympani, at whose bottom it finally surges against the membrane covering the fenestra rotunda; or the wave may be transmitted directly across the membranous cochlea. The fluids of the labyrinth being physically incompressible, the function of the fenestra rotunda as a sort of safety-valve seems evident. Politzer inserted a glass tube in the round window, and found that fluid in the tube rose when strong air-pressure was brought to bear on the outer side of the tympanic membrane. The cavity

of the membranous labyrinth (Pl. 2, Fig. 4) is nowhere in communication with the perilymph-space about it, and we must therefore assume that the irritation of the auditory cells seated in its wall must depend on vibrations transmitted from the perilymph directly through the membranous sacs and tubes.

Like the perilymph-space, the cavity of the membranous labyrinth is in communication throughout, though in certain situations the connection of adjacent parts is very indirect. Thus, though the semicircular canals open freely at both ends into the utricle, the utricle and saccule are only brought into union by the two narrow tubes that unite to form the ductus endolymphaticus. It will be noted that by means of this duct the membranous labyrinth is really continued into the cranial cavity. The saccule in turn is continuous with the scala media of the cochlea by way of the canalis reuniens.

The Membranous Cochlea and the Organ of Corti (Figs. 280–282).— The cochlear division of the auditory nerve, together with the nutrient blood-vessels, penetrates the modiolus at its base and runs up through the spongy interior of the bony pillar. As the nerve ascends through the modiolus its fibres are gradually all diverted to run in a radial direction between the bony plates of the lamina spiralis, to terminate in the *organ of Corti* of the canalis cochlearis. A collection of nerve-cells is interposed in the course of the auditory fibres at the base of the *lamina spiralis*.

A complete view of the nerves of the cochlea would show a central pillar of nerve-fibres diminishing in thickness from below upward, and winding round this pillar a spiral sheet of radially-disposed nerve-fibres containing, near their point of departure from the central pillar, a spiral line of ganglion-cells; this collection of cells is therefore known as the *ganglion spirale*. The thin, free edge of the bony *lamina spiralis* is, in the recent state, thickened by a development of connective tissue forming a promontory known as the *limbus*. The free edge of the *limbus* is in turn shaped in such a way as to make a short, sharp projection in the plane of the upper surface of the lamina and a longer projection in the plane of its lower surface, leaving the free margin between them hollowed out. The upper projection, which is known as the vestibular lip, *labium vestibulare*, serves for the attachment of the tectorial membrane, *membrana tectoria*, presently to be described. The lower projection is called the tympanic lip (*labium tympanicum*); to it is attached the inner margin of the basilar membrane, on whose inner half is seated the very complex structure known as the organ of Corti.

The *basilar membrane* is a thin sheet of fibrillated connective tissue stretched tightly between the tympanic lip of the limbus on the inside and the spiral ligament (see p. 824) on the outside. The more median part of the membrane, which supports the organ of Corti, is thin and rigid and is fibrillated in a radial direction. The outer part, which is first thicker and then thinner again near its point of attachment, is distinctly composed of radial fibres cemented together; the isolated fibres are characterized by being stiff and brittle.

The *organ of Corti* (Figs. 280, 281) has as its supporting basis a series of peculiarly modified epithelial cells, known as the *rods of Corti* (Fig. 282, B, B'),

which are disposed along the edge of the spiral lamina in two rows, an inner and an outer. The inner rods have their feet on the basilar membrane near its median attachment; they lean outward and upward, and at their upper extremity join or articulate with the heads of the outer rods, whose feet are fastened to the basilar membrane more externally. The two rows of rods are thus joined together like the rafters of a house, and enclose beneath them a canal known as the *tunnel* of the organ of Corti. The inner rods are more numerous than the outer, so that the latter are fastened rather between than to the ends of the former. Leaning against the inner or median side of the inner row of rods is a single row of hair-cells (Fig. 281), much like those described as seated on the maculæ and cristæ of the labyrinth, to which hair-cells filaments of the
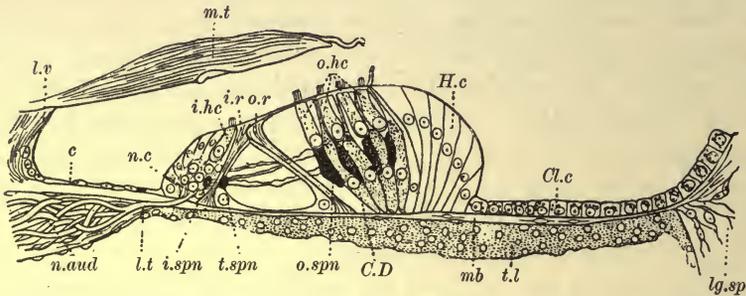
FIG. 281.—Diagram of the organ of Corti (from Foster, after Retzius): *i.r*, inner rod of Corti; *o.r*, outer rod of Corti; *i.hc*, inner hair-cell; *n.c*, the group of nuclei beneath it; *o.hc*, outer hair-cells, or cells of Corti; *C.D*, the twin cells of Deiters (four rows); *n.aud*, the auditory nerve perforating the tympanic lip, *l.t*, and lost to view among the nuclei beneath the inner hair-cells; *i.spn*, the inner spiral strand of nerve-fibrils; *t.spn*, the spiral strand of the tunnel; *o.spn*, the outer spiral strand belonging to the first row of outer hair-cells; the three succeeding spiral strands belonging to the three other rows are also shown; nerve-fibrils are shown stretching radially across the tunnel; *H.c*, Hensen's cells; *Cl.c*, Claudius' cells; *t.l*, lymphatic epithelioid lining on the side toward the scala tympani; *lg.sp*, ligamentum spirale; *c*, cells lining the spiral groove, overhung by the vestibular lip, *l.v*; *m.t*, tectorial membrane; a fragment, torn from it, remains attached to the organ of Corti just outside the outermost row of hair-cells.

auditory nerve are distributed. Closely applied to the single row of hair-cells, on the inner side, are several rows of columnar cells gradually decreasing in size toward the median line, and beneath the whole is a group of nuclei. External to the outer row of rods, and separated from it by a space, are four parallel rows of hair-cells known as the *cells of Corti*; their bodies do not reach downward as far as the basilar membrane, and just below each row is a bundle of nerve-fibres which have traversed the tunnel of Corti and then have changed their direction from a radial to a longitudinal or spiral one. These fibres, and others having a more direct course, one by one end in clusters encircling the individual hair-cells.

Four rows of peculiarly-modified columnar cells, the *cells of Deiters*, are inserted closely between the cells of Corti, the outermost row being external to the fourth row of Corti. These cells rest below on the basilar membrane. Still external to these groups of cells is a series of rows of tall columnar cells of simple character supported upon the basilar membrane, and rapidly decreasing in height externally into a layer of cuboidal epithelium covering the outer part of the basilar membrane. The rods of Corti are peculiarly shaped at the

top, the upper extremity of each being bent at an angle so as to project exter-
nally and parallel with the basilar membrane; these projections are the *pha-
langar processes* of the rods, the *phalanges* of the inner row overlapping those
of the outer row. These phalangar processes of the rods form the points of
attachment—in fact, the beginning—of the *reticulate membrane (membrana
reticulata)*, a peculiar cuticular, network-like structure formed of rings and
cross-bars, having the appearance of certain vegetable tissues seen under the
microscope. The reticulate membrane stretches across the outer rows of hair-
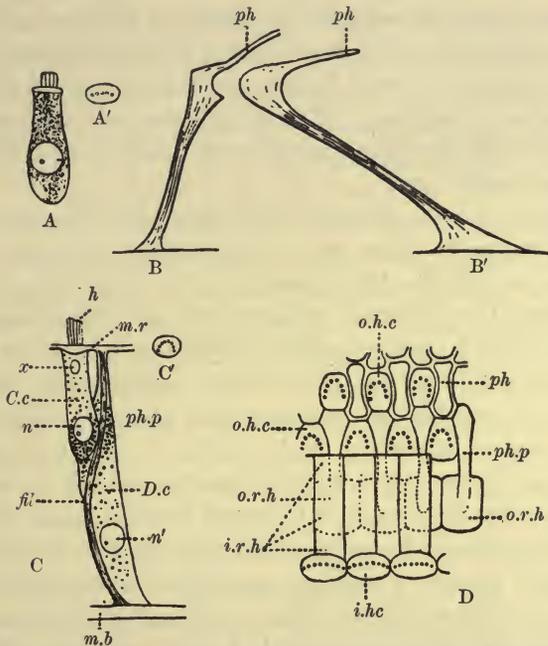
FIG. 282.—Diagram of the constituents of the organ of Corti (from Foster, after Retzius): A, inner hair-cell; A′, the head, seen from above; B, inner, B′, outer, rod of Corti; *ph*, in each, is the phalangar process; C, the twin outer hair-cell; *C.c*, the cell of Corti; *h*, its auditory hairs; *n*, its nucleus; *x*, Hensen's body; *D.c*, cell of Deiters; *n′*, its nucleus; *ph.p*, its phalangar process; *fil*, the cuticular filament; *m.b*, basilar membrane; *m.r*, reticulate membrane; *c′*, the head of a cell of Corti, seen from above; D, the organ of Corti, seen from above; *i.hc*, the heads of the inner hair-cells; *i.r.h*, the head and phalangar process of the inner rod; *o.r.h*, the head of the outer rod, with *ph.p*, its phalangar process, covered to the left hand by the inner rods, but uncovered to the right; *o.h.c*, the heads of the cells of Corti, supported by the rings of the reticulate membrane; *ph*, one of the phalangæ of the reticulate membrane.

cells, the body of each of which is enclosed and is held at its top within a ring
of the network (Fig. 282, D).

Each of the cells of Deiters, described above, is continued upward in a
process which is attached to a cross-bar or a ring of the reticulate membrane
next outside its companion-cell of Corti. The inner or median line of the
Deiters cell is also modified into a cuticular thread fused below to the basilar
membrane and above to a ring of the reticulate membrane. Thus the audi-
tory hair-cells of Corti may be regarded as suspended from the reticulate mem-
brane, which in turn is supported by the cuticular processes of the cells of
Deiters, which rest upon the basilar membrane, and by the phalangar pro-

cesses of the rods of Corti. The physical contact of the cells of Corti with those of Deiters is so intimate—if, indeed, their substance is not continuous— that impulses generated in the one can probably easily be communicated to the other.

The upper wall of the canalis cochlearis is made of a sheet of homogenous, fibrillated connective tissue covered with flat cells, and stretches from the limbus of the spiral lamina outward and upward to the side wall of the cochlea. It is known as the *membrane of Reissner*. The periosteal connective tissue of the bony wall of the cochlea is generally well developed within the area enclosed between the membrane of Reissner and the membrana basilaris; it is particularly thick at the line of division between the scala media and the scala tympani, where it forms a projecting ridge at the outer attachment of the basilar membrane. This ridge is the *spiral ligament;* an extension from it, gradually decreasing in thickness, reaches into both the vestibular and the tympanic scala.

A thick layer of both columnar and cuboidal epithelium lines the connective tissue forming the outer wall of the canalis cochlearis. This epithelium is peculiar in that the blood-vessels of the underlying connective tissue penetrate between the epithelial cells themselves. The *tectorial membrane* (*membrana tectoria*) is a sheet of radially-fibrillated tissue, thin at its point of attachment to the vestibular lip of the limbus, and becoming thicker and then thinner again as it stretches out over the organ of Corti, reaching as far as the most external row of hair-cells. It is said to lie in actual contact with the rods of Corti and the free ends of the hair-cells, and it has been presumed to serve as a damper for the vibrations imparted to the organ of Corti.

Theory of Auditory Sensation.—It may now be mentioned that the generally-accepted theory of auditory sensation, as concerned with impulses generated in the cochlea, supposes that the vibrations of the perilymph, the endolymph, or of both are imparted to the basilar membrane. This membrane, from its fibrillated structure, may perhaps rightly be regarded as a sheet of parallel wires like those of a piano-board. As the wires of a piano have different rates of vibration according to their length, and respond sympathetically to correspondingly different notes sounded in their neighborhood, so it has been supposed that different radial fibres of the basilar membrane are set into sympathetic vibration by different rates of vibration in the fluids bathing them. These vibrations must be imparted to the structures in the organ of Corti, and the irritation of the nerves connected with the cells of Corti is a natural sequel. It may be repeated that, though the canal of the bony cochlea as a whole diminishes in diameter from base to cupola, the canal of the membranous cochlea, the scala media with its lower wall or basilar membrane, increases in diameter. Thus the radial fibres of the basilar membrane are longest near the apex of the cochlea. The radial width of the basilar membrane, measured near the bottom, middle, and top, respectively, is given as .21 millimeters, .34 millimeters, and .36 millimeters. The number of fibres of the basilar membrane is said to be 24,000; the number of inner hair-

cells, 3500, and of outer hair-cells in four rows, 12,000; outer rods of Corti, 3850; and inner rods of Corti, 5600.

C. The Relation between Physical and Physiological Sound.

Production of Sound-waves.—Sound, in its physiological meaning, is a sensation which is the conscious appreciation of internal changes occurring in certain cells of the cerebral cortex. Fibres of the auditory nerve come into close relation with these cells, and in whatever way those fibres are excited the result is one and the same, a sensation of sound.

The elaborate apparatus of the middle and internal ear is so constructed that the energy of mechanical oscillations in the external air is transmitted to the terminations of the auditory nerves in a manner to excite them.

Sound, in a physical sense, consists in waves of alternate condensation and rarefaction travelling in the air from the point of origin of the sound, much as waves radiate over the surface of water from the point where a stone is dropped. Any sudden impulse, such as a puff of air, or the vibration of a solid body, as a stretched string or a tuning-fork, pushes the adjacent molecules of air against those further removed, and this impulse produces an area, or aërial shell, of increased density or condensation. The air being perfectly elastic, the molecules, relieved from pressure, spring back even beyond the position of equilibrium, and leave an area of decreased density or rarefaction. Thus a wave, consisting of a shell of condensation succeeded by a shell of corresponding rarefaction, moves through the air. This single air-wave is the simplest element of physical sound. When a number, no matter how great, of sound-waves simultaneously excite the same particle of air, the resultant motion of that particle is the algebraic sum of all the motions imparted to it by the single sound-waves considered separately. As any elastic body, when set vibrating, continues its oscillations for a time, so is it probable that strictly isolated air-waves do not occur. Any elastic body, such as a stretched string, or a tuning-fork, when set in vibration, sends out from itself a series of air-waves which succeed one another at a rate identical with the rate of vibration of the elastic body. Such a regular succession of air-waves striking upon the tympanic membrane sets the latter into correspondingly regular oscillations and produces in the auditory apparatus the sensation of *musical tone.*

Loudness and Musical Pitch.—The more vigorous the vibrations of the oscillating body, the more forcibly are the air-molecules which are struck by it driven forward; and the greater their excursion or *amplitude* of movement, the greater is the force with which the tympanic membrane is driven inward when the moving air-wave strikes it. The *loudness* of the tone manifestly depends upon the extent of motion of the tympanic membrane, as does this on the *amplitude* of air-motion. Different elastic bodies have different natural rates of oscillation. The more rapid the rate, the more frequent is the succession of air-waves that strike upon the ear. Musical *pitch* is determined by the number of air-waves which pass a given point in a unit of time, or, in other words, by the rate of vibration of the sound-producing body. When

the vibration-rate increases the pitch is elevated, and *vice versâ*. If some body capable of producing sound should have its rate of vibration changed gradually from 5 or 10 vibrations per second to 50,000 per second, no sensation of sound would be aroused until the vibrations reached the rate of about from 16 to 24 per second. The droning note of the 16-foot organ-pipe and the lowest bass of the piano represent a vibration-rate of 33 per second. In most persons sounds cease to be audible when the air-waves have a frequency of 16,000 per second, though to some the note produced by 40,000 vibrations is perceptible. It seems clear that some animals hear tones whose pitch is so elevated as to make them inaudible to human ears. When a moving bell or whistle, as of a locomotive, rapidly approaches, its pitch seems to rise, and then to fall as it recedes. The reason for this variation is that the motion of the locomotive adds to or subtracts from the number of sound-waves reaching the ear in a given time. In musical execution and in the ordinary uses of life the limits in the pitch of sounds are much narrower. Thus, as just stated, the lowest bass of the piano (C_1) represents a vibration-rate of 33 in a second, while the highest treble (c'''''') has that of 4224. As to the absolute number of vibrations necessary to produce the sensation of sound, it has been found that 2 or 3 vibrations excite the sensation of a mere stroke; 4 or 5 vibrations are necessary to give a tone; and some 20 or 40 are required to develop the full musical qualities of a tone.[1] That is to say, when a musical tone falls upon the ear its characteristics cannot be appreciated until 20 to 40 vibrations have been completed.

Thus, from a physical scale representing aërial vibrations of indefinitely various rapidity the mind selects and appreciates as *sound* a very small fraction.

Tympanic Membrane as an Organ of Pressure-sense.—There is good reason to suppose that variations in air-pressure succeeding one another too slowly or too irregularly to produce sound-sensation are still of great importance in the extensive realm of sensations which but obscurely excite our consciousness. Slow inward movements of the tympanic membrane may still give rise to a perception of external changes. Thus, a blind man has been able to say correctly that he has passed by a fence, and whether it be of solid board or of open picket. If any one with closed eyes holds a book at half-arm's length in front of the ear, a different sensation will be experienced according as the book is turned flat or edgewise to the face; the feeling is one of "shut-in-ness" or "open-ness," respectively. The air is in ceaseless agitation, and its waves, striking against various objects, must be reflected to the ear with an intensity dependent on the position and the physical character of the reflecting media. We may assert that the tympanic membrane is the peripheral organ of a *pressure-sense* by which we become more or less accurately aware of the nature and position of surrounding objects, irrespective of the sensations of sight and hearing. Whether that group of sensations depends on the excite-

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[1] Mach: *Physikalischen Notizen Lotos,* Aug., 1873; V. Kries und Auerbach: *Du Bois-Rey-mond's Archiv für Physiologie,* 1877, p. 297; Helmholtz: *Sensations of Tone,* translated by Ellis.

ment of tactile nerves in the tympanic membrane or of the auditory filaments in the internal ear is yet uncertain.[1] Such sensations probably form an important quota of that complex system of sensations which do not obtrude themselves on consciousness, but which, nevertheless, bring information from the outer world, and have an intimate association with the more or less reflex movements that preserve the equilibrium of the body.

Overtones and Quality of Sound.—We have thus far considered only simple tones produced by simple vibrations of elastic bodies. Thus, a stretched string plucked at its middle vibrates throughout its whole length, the greatest amplitude of movement being at the middle point, which moves to and fro like a pendulum. It is very rare that a body set vibrating confines itself to a single pendular movement. Thus, a stretched string when struck not only moves as a single cord, but the string may break up, as it were, into two halves, each vibrating independently, but with twice the rate of movement of the whole length of string. Not only is this the case, but the string in its vibration also breaks up into chords of one-third, one-fourth, one-fifth, etc. of its original length, giving rise to vibrations three, four, and five times as rapid as those produced by the whole string. In musical phrase, the middle *c* of the piano, when this key is struck, gives not only a note *c* representing 132 vibrations, but also its octave *c'* of 264 vibrations, the fifth above this of 396 vibrations, the second octave, 528, the third above this, 660, and so on. The vibration of a string, then, sends to the ear a complex series of tones each of which represents a simple pendular motion of the air. The lowest tone, that produced by the slowest rate of vibration of the string as a whole, is known as the *fundamental tone*.

The pitch of the fundamental tone determines our estimate of the pitch of the whole complex note. The other tones produced by segmental vibration of the string are known as *partial tones, upper partials*, or *overtones*. The fundamental tone is usually stronger than its accompanying overtones, the successively higher upper partials diminishing rapidly in intensity. Some musical instruments produce notes with a longer series of overtones than do others; the human voice is particularly rich in overtones. Instruments differ also in the greater or lesser strength and in the relative prominence of the individual overtones accompanying the fundamental. *It is the number and the relative prominence of the overtones in a musical note that determine its quality.* Thus, a violin, a cornet, and a piano, though sounding a note of the same pitch, would never be mistaken the one for the other; our discrimination of their notes depends simply upon the difference in the relative strength and the number of their overtones, the fundamental tone being the same throughout. The brilliancy and richness of musical notes is dependent on their wealth of upper partials. It is believed that a sound-producing body, like a stretched string, does not send to the ear a separate set of waves representing each of its segmental vibrations, but that all the waves aroused by it fuse together into a single series of waves of peculiar form. Such a composite wave may be

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[1] W. James: *Psychology*, 1890, vol ii. p. 140.

represented graphically by depicting under one another a series of waves having two, three, four, etc. times the rate of succession of the curve indicating the fundamental tone. If a vertical line be drawn across the series representing the vibration-rates of the various tones, and an algebraic addition be made of the distance of each point of intersection above or below the line of rest, the result will determine the position of the composite curve on the same vertical (Fig. 283). It is evident that the form of the composite wave must change with every change in the number and relative prominence of musical overtones, and the movement imparted by it to the tympanic membrane and the wave
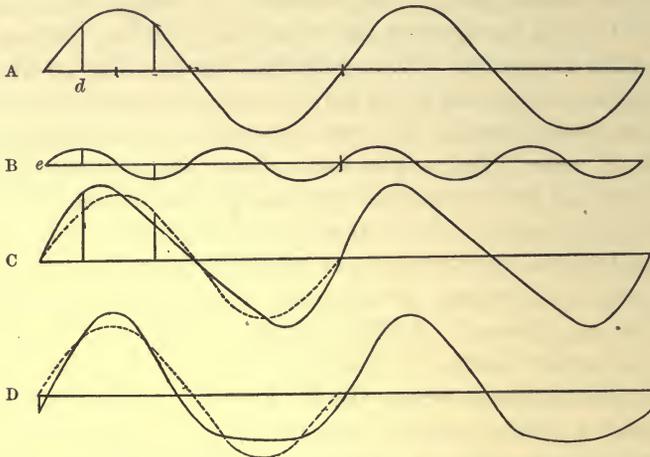
Fig. 283.—The curve B represents twice the vibration-rate of A. When the two curves are combined by the algebraic addition of their ordinates, the result is the periodic curve c (solid line), having a different form ; the dotted line of c is a reproduction of A. If B is displaced to the right until e falls under d in A (change of phase), the combination of A and B will give the curve D, the dotted line in D representing A as before.

generated in the perilymph must have corresponding differences. Notes of different quality are produced by composite air-waves of different forms. But waves differing in form may still produce notes of the same quality ; for if, in the graphical figure, one or more of the curves representing simple tones be slid to the right or the left, the form of the composite wave will thereby be changed, but not the quality of the sound produced by it. In other words, change of phase of the partial tones does not alter the quality of the note.[1] The quality of any complex note may be reproduced by sounding together a series of tuning-forks which have, respectively, the vibration-rate of the fundamental tone and that of one of the overtones of the complex note.

Analysis of Composite Tones by the Ear.—According to the theory outlined on page 824, the composite wave, beating against the sensitive organ of the cochlea, is again analyzed into the elements composing it, one part of the basilar membrane vibrating sympathetically with one partial tone, another with another. The isolated irritation of each nerve-element arouses in the mind the idea of a tone of a certain pitch and loudness ; but when a number

[1] Helmholtz, *op. cit.*, pp. 30–34.

of such elements are simultaneously stimulated, the mind takes note, not of the individual sensations thereby aroused, but of a resultant sensation formed by the fusion of these.

That apparently simple tones are actually made up of a number of partials, having rates of vibration which form simple multiples of the fundamental tone, may easily be demonstrated at the open piano. If any note, as c in the bass clef, be struck while the key of its octave c is depressed, and then the struck string be damped, it will be found that the octave c rings out with its proper note. So in turn the *g* above that, the second octave and the *e* above that, may be made to sound when the lower c is struck, because each of these strings is so tuned that its fundamental note has the same vibration-rate as one of the overtones of the lower c. A note sung near the piano may in the same way be analyzed more or less completely into its component tones. The organ of hearing certainly has some such power of musical analysis, for some cultivated ears can not only follow any special instrument in a playing orchestra, but can even distinguish the overtones in a single musical note.

The ear has little or no power of distinguishing difference of pitch in tones of less than 40 or more than 4000 vibrations per second; but in the upper median parts of the musical scale the sensitiveness to change of pitch is very acute. Thus, according to Preyer,[1] in the double-accented octave a difference of pitch of one-half vibration in a second can be detected; that is, in the octave included between 500 and 1000 vibrations per second, 1000 degrees of pitch can be perceived.

Every elastic body is capable of *sympathetic vibration;* that is, air-waves beating upon it at its own natural rate of vibration set it into corresponding motion. In the same manner a heavy pendulum may be forced into violent movement by exceedingly light taps with the finger, the only necessary condition being that the impulses imparted by the finger be exactly timed to the periodic motion of the pendulum or to some multiple of it. A body capable of sympathetic vibration with some particular tone is set into vibration by that tone, and reinforces or magnifies it, whether the tone exists alone or as the fundamental of a complex note, or is contained in the latter simply as an upper partial.

The analysis of musical sounds is usually carried out by the use of resonators, which are hollow cylinders or spheres of glass or of metal, rather widely open at one pole, and narrow-pointed at the opposite end for insertion into the ear. The mass of enclosed air vibrates, according to its size and shape, at some particular rate, and it is very readily set into sympathetic vibration whenever its fundamental tone is contained in any sound reaching it. By this means it is possible strongly to magnify, and thus select, the individual overtones contained in a note. The vowel sounds of human speech owe their difference of quality to the adjustment in size and shape of the resonant air-chambers above the vocal cords.

[1] *Ueber die Grenzen der Tonwahrnehmung,* June, 1876.

Inharmonic Overtones.—It will be remembered that all the overtones contained in a musical note are produced by vibrations which are simple multiples of the rate of the fundamental tone. These overtones are properly called *harmonic* upper partials; they are, according to Helmholtz, particularly characteristic of stretched strings and narrow organ-pipes. But most elastic bodies have proper tones which are not exact multiples of the fundamental, and which may be termed *inharmonic* upper partials. The high-pitched jingle heard when a tuning-fork is first struck represents the inharmonic upper partials of the fork. Stretched membranes have a great number of such inharmonic overtones. Inharmonic upper partials, as might be expected, rapidly die out in a note of which they form a part. It is evident that inharmonic proper tones, when nearly of the same pitch, must interfere with one another and repress the development of a well-marked fundamental tone.

Production of Beats.—When two tones of slightly different pitch are sounded together, the more rapid vibrations overtake the slower, so that at certain periods the crests, or phases of condensation, of two waves fall together, and the result is a phase of increased condensation and louder sound. The waves immediately cease to correspond, and diverge more and more until the crest of one falls upon the trough of another, the result being silence, or at least great diminution in the intensity of the sound. Such alternate augmentation and diminution of the waves give rise to pulses in the sound, known technically as *beats*. This is one of the most familiar and important phenomena of musical art. If two tuning-forks on resonance-boxes vibrate in unison, a piece of wax stuck to the prong of one fork will lower its tone and give rise to beats. The undulating sound caused by striking a bell or the rim of a thin glass tumbler is due to beats. When two notes not included in a perfect chord are sounded on the piano, beats are heard not only from the interference of the fundamental tones, but of the upper partials as well. It is the absence of beats in notes which should be in harmony, as those of the major chord, that determines the instrument to be in tune. When two tones produce beats, the number of beats in a given time is equal to the difference between the number of vibrations involved in the two tones in the same time. For example, a tone produced by 256 vibrations in a second sounded with one of 228 vibrations would give 28 beats in a second. It is evident that the frequency of beats may be increased either by increasing the interval between the tones or by striking tones of the same interval in a higher part of the scale. Beats which are not too frequent—from four to six in a second—have important musical value, but when they number thirty or forty in a second they become exceedingly disagreeable, irritating the ear in a manner analogous to the effect of a flickering light on the eye. When sufficiently near together the beats no longer produce an intermittent sensation. The number of beats in a second required to result in this fusion increases as we ascend the musical scale, varying from 16 beats at c of 64 vibrations per second to 136 beats at c''' of 1024 vibrations.[1] The reason for this variation lies in the progressive shortening of the waves as the

[1] Mayer: *Sound*, 1891.

sound becomes higher in pitch; for it is obvious that as we ascend the scale, and the waves of sound become progressively shorter, spaces would be left between the individual waves unless their number were proportionately increased.

Harmony and Discord.—Tones are *concordant*, or *harmonize*, when they produce no beats on being sounded together; they are *discordant* when beats are produced, and the painful sense of dissonance increases in intensity up to about 33 beats per second. Perfect concord is obtained by blending notes whose vibrations are to each other as small whole numbers.

Thus, in the major cord	C	E	G	c
the vibration-numbers are	132	165	198	264
their ratios are	4	5	6	8

If notes the ratios of whose vibration-rates can be represented only by large whole numbers are combined, a discord is formed, for the reason that their upper partials interfere with one another and cause beats; there is no especial virtue in the small integer.[1]

Thus, in the discord	C	D	E
the vibration-numbers are	132	148.5	165

which are not reducible to small whole numbers.[2]

Combinational Tones.—When two tones are sounded together, there is produced a new, usually weaker, tone, whose vibration-number is the numerical difference between the vibration-rates of the original tones. It is therefore known as a *differential tone*. Such tones may arise from upper partials as well as from the fundamentals; they do not appear to be formed, as might be supposed, by the fusion of beats. Other "combinational" tones of more intricate relations, as well as beats, arise from the interaction of vibrations when many different notes, as those of an orchestra, are sounded together. To calculate the physical result of the combination of these impulses, which it is the duty of the tympanic membrane to transmit, is a problem of exceeding complexity.

Résumé.—To sum up the subject, musical sounds are distinguished in sensation by the three factors, *loudness*, *pitch*, and *quality*, sometimes called *color* or *timbre*. These sensations depend in turn on definite physical characters of air-waves: their *amplitude*, or the extent of motion of the air-molecules; their *frequency*, or rate of succession of the waves; their *form*, which is determined by the pitch and relative predominance of the upper partials combined with the fundamental tone.

Fatigue.—That the ear is subject to fatigue toward a note that has been sounded is easily demonstrated in the following way: Strike a single note of, say, a major chord on the piano, and immediately afterward sound the full chord; the quality of the latter will be altered from its normal character, owing to the lessened prominence of the note which had been struck.[3] We may therefore not improperly speak of a successive contrast in auditory sensa-

[1] Tyndall : *Sound.*   [2] Waller : *Human Physiology*, 1891.
[3] Foster : *Text-book of Physiology*, 5th ed., 1891.

tions, analogous to visual successive contrast, by which our perception of every sound is colored by the sounds which have preceded it.

Imperfections of the Ear.—Notwithstanding the mechanical provisions for making the external and middle ear a perfect transmitting apparatus, sound-perception is more or less modified by the action of the mechanism under certain conditions. Thus, Helmholtz believed that various combinational tones owe their origin chiefly to a periodic clicking in the joint between the malleus and incus bones. The resonance of the ear is a familiar fact, and through it high-pitched tones between e'''' and g'''' are reinforced and heard with undue loudness. Certain hissing sounds, the chirp of a cricket or the note of a locust, thus gain their intensity. This resonance probably is a feature of the external auditory meatus, since it is at once destroyed by applying a small resonator to the ear (Helmholtz).

Perception of Time Intervals.—The ear is eminently the sense apparatus for determining small intervals of time. Flashes of light succeeding each other at the rate of twenty-four in a second are fused in a continuous luminous impression by the eye, but by the ear at least one hundred and thirty-two auditory impulses as beats may be heard separately in a second. The power which the ear possesses of resolving complex air-waves into the host of pendular vibrations which may enter into their formation finds no analogy in the eye (Helmholtz).

Musical Tones and Noises.—The important feature of the physical processes which give rise to musical tones is their *periodicity*. Every musical tone is produced by a regular succession of alternate rarefactions and condensations in the air. The remaining class of sounds, known as *noises*, differs from musical sounds in the respect that such sounds are produced by an irregular succession of air-waves—one in which the interval between phases of condensation and rarefaction does not remain constant as in a musical note. Noises are for the most part made up of short musical notes so associated as not to "harmonize" with one another. As expressed by Helmholtz, the sensation of a *musical* tone is due to a rapid *periodic motion* of a sonorous body; the sensation of a *noise*, to *non-periodic* motions.

Functions of Different Parts of the Ear.—Concerning the functions of the different parts of the internal ear in their relation to sound-perception, it is generally believed, as previously stated, that the basilar membrane of the cochlea, with the nervous elements seated on it, is the organ concerned in the reception and transmission of musical sounds. There are a sufficient number of fibres in the basilar membrane to allow several to vibrate with every audible tone.

It cannot, however, too strongly be impressed that no theory of physiological action should be accepted definitively without rigid experimental proof, and such evidence concerning the definite functions of the cochlea is almost wholly wanting. The sensory hair-cells on the maculæ of the saccule and the utricle have been thought to have the duty of vibrating in response to any agitation imparted to the perilymph, without regard to its periodic character; they

might thus be termed sense organs for the perception of noises. Evidence will be adduced later (p. 848) for the belief that they are peripheral organs for the preservation of static equilibrium.

The hair-cells on the cristæ of the ampullæ of the semicircular canals seem to have a special function in giving rise to sensations caused by changing the position of the head ; they thus are organs concerned with the preservation of the equilibrium of the body.

Judgment of Direction and Distance.—The distance and direction from which sounds come to the ear are not perceived directly, but our estimate of them is a judgment based on the loudness and quality of the sound sensation, combined with a power of reasoning from past experience. Thus, in seeking to discover the direction whence a sound comes, it is usual for an observer to turn

Fig. 284.—End-bulbs from human conjunctiva (from Quain, after Longworth) : A, ramification of nerve-fibres in the mucous membrane, and their termination in end-bulbs, as seen with a lens ; B, end-bulb, highly magnified ; *a*, nucleated capsule ; *b*, core, the outlines of its component cells not seen ; *c*, entering nerve-fibre branching, its two divisions to end in the bulb at *d*.

the head to the position in which the sound is heard loudest, and thus to form an opinion as to the direction whence it comes. Errors of judgment as to the direction are frequent, owing to the sound reflected from some object appearing louder than that coming in a direct line from its source. It is said that when there is total deafness in one ear every sound seems to have its origin on the side of the healthy ear. The quality as well as the loudness of a sound varies according to the distance of its source. Thus, the lower tones die away earliest as a sound recedes, bringing the overtones into undue prominence. The art of the ventriloquist consists largely in altering the quality of the sounds he produces to imitate the quality they would naturally have if arising under the conditions which he would lead his hearers to believe to be their origin. A comparatively feeble sound near at hand may have the same quality as a loud

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one heard at a distance; thus, a frog croaking in an adjoining room was once mistaken by the writer for a large dog barking outside the building.

D. CUTANEOUS AND MUSCULAR SENSATIONS.

General Importance of the Cutaneous and Muscular Sensations.— Cutaneous sensations are aroused by the operation of some form of energy on the skin, and they include the sensations of *touch*, of *temperature*, and of *pain*. By *muscular sensation* is meant the appreciation which we have of the intensity and direction of muscular effort. Closely allied to this sensation is a *general sensibility* through which we gain a knowledge of the relative position of the parts of our bodies, irrespective of movements. The direction, size, distance, and surface features of external objects are usually made known to us through the sense of
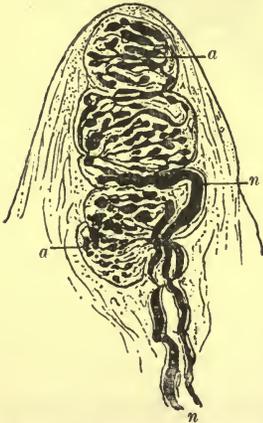
FIG. 285.—Tactile corpuscle within a papilla of the skin of the hand (from Quain, after Ranvier): *n, n*, two nerve-fibres passing to the corpuscle; *a, a*, terminal varicose ramifications of the axis-cylinder within the corpuscle.
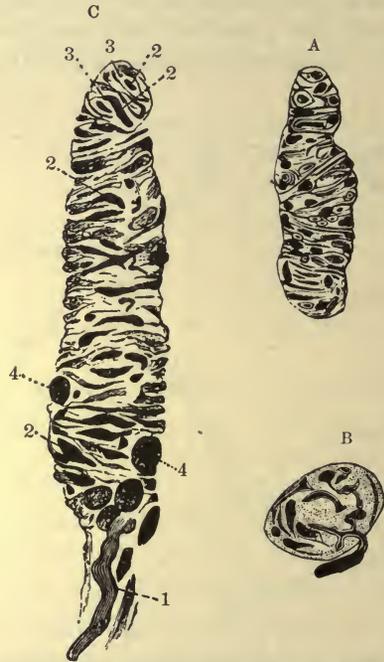
FIG. 286.—Other tactile corpuscles (from Quain; A, B, after Meckel; c, after Fischer): A, longitudinal section showing the interior traversed by connective-tissue septa derived from the capsule; the nerve-fibres are cut across. B, transverse section at the point of entrance of a nerve-fibre, showing the axis-cylinder branching; other fibres cut obliquely. c: 1, entering nerve-fibre, medullated; 2, 2, the same cut variously within the corpuscle; 3, 3, clear spaces around the fibres; 4, 4, nuclei of the transverse and spirally-disposed cells of the corpuscle.

sight or of hearing. Yet these fundamental facts regarding the things about us do not become a part of knowledge through direct visual and auditory perception. Such knowledge is based on complex judgments concerning the meaning of auditory and visual phenomena according as they have, in past experience, been interpreted by tactile and muscular perceptions. That is, when reduced to its simplest terms, our most practical and important knowledge of the world is the outgrowth of tactile and muscular perceptions; by and with them all other sense-perceptions of objects have been corrected and compared. Thus, so simple a feat as the estimate of the size of a distant object is

the result of a complex judgment based on tactile and muscular experience. Through the sense of sight we perceive the ratio of the visual angle subtended by the object to that of the whole field of vision; but as objects of different size may fill the same visual angle when at different distances from the eye, our estimate of their size depends upon the distance at which we suppose them to be situated. The distinctness of the surface features of the body afford the mind an important clue, since experience shows that details of surface in a body become more obscure as we recede from that body. But more important data concerning distance come from the sense of muscular innervation, or feeling of the intensity of muscular contraction, by which we estimate the degree of convergence of the optic axes when the object is focussed, and still more by the perception of the amount of muscular effort necessary to sweep the optic axes over the ground surface intervening between the observer and the object. When objects approach the near-point of vision the sense of innervation of the pupillary muscles affords important evidence of their distance.

That fundamental education concerning the outer world which engages the earliest years of every child consists in accumulating and systematizing with other sense-perceptions tactile and muscular impressions of objects. A sensation is no sooner felt than some muscular movement involving a definite muscular feeling is made by which the character of the sensation is changed and experimentally tested under different conditions. The physiological process involved in building up sense-knowledge, therefore, embraces in alternation sensation excited by external objects, motion accompanied by muscular sensation, and change in the original sensation. In other words, the motor and sensory impulses form a sort of balance, and both are necessary.

Ending of Sensory Nerve-fibres in the Skin.— The afferent nerves supplied to the skin have several modes of termination. In the commonest form the plexus of medullated nerve-fibres found in the dermis

FIG. 287.—Magnified view of a Pacinian body from the cat's mesentery (from Quain, after Ranvier): *n*, stalk with nerve-fibre enclosed in sheath of Henle, passing to the corpuscle; *n'*, its continuation through the coil, *m*, as a pale fibre; *a*, termination of the nerve in the distal end of the core (the terminations are not always arborescent); *d*, lines separating the tunics of the corpuscles; *f*, channel through the tunics, traversed by the nerve-fibre; *c*, external tunics of the corpuscle.

close under the epidermis gives off twigs which, losing the medullary sheath, pierce the epidermis and here form a network among the cells of the Malpighian layer, the single fibres ending freely in this position (Fig. 294). Other sensory nerves do not penetrate the epidermis, but end in various peculiar terminal organs in the dermis or in the subcutaneous tissue underneath. These terminal organs are known respectively as *end-bulbs, touch-corpuscles,* and *Pacinian bodies* (Figs. 284–287). Each organ consists of a more or less conical body in which a nerve-fibre terminates. The *end-bulbs* are found only on the

dermis of the conjunctiva and the lips, and in modified form on the sensitive surfaces of the genital organs (Fig. 284). The *touch-corpuscles*, though apparently absent from the greater part of the body, occur in great numbers in the skin of the palmar surface of the hand and that of the fingers, especially at their tips; at the edge of the eyelids and the lips; on the soles of the feet and the toes; and on the surface of the genital organs. The touch-corpuscle often occupies a papilla of the dermis directly under the epidermis (Fig. 285). The *Pacinian bodies*, which are oval corpuscles, larger than the foregoing, and easily visible to the unaided eye, are found not in the skin proper, but in the subcutaneous connective tissue beneath it. They are found in abundance beneath the skin of the palm of the hand and the sole of the foot; they are also numerous along the nerves of the joints, and even among the sympathetic nerves supplying the abdominal organs (Fig. 287). Sensory nerves also end in tendons as somewhat arborescent expansions of axis-cylinder matter known as the *organs of Golgi*, and in muscles near their tendinous attachments.

1. **Sense of Touch.**—*The Relations between Sensation and Stimulus.*— Many so-called "tactile sensations," such as wetness, hardness, roughness, etc., are not simple sensations at all, but are complex judgments built up out of the association of certain tactile, temperature, and muscular sensations, and conveying to us a knowledge of the surface, substance, and form of bodies.

When analyzed, the sense of touch is nothing more than a sense of *pressure* applied to the skin. To test the *pressure sensibility* of the skin the object whose weight is to be estimated must not be lifted in the ordinary way, for that would bring into play the muscular sensations. If the skin of the hand is to be tested, the hand must be placed upon some firm support, such as a table, and the weights be laid upon the skin. The smallest perceptible weight that can thus be felt varies with the situation to which it is applied. Thus, the greatest sensitiveness to pressure is found on the forehead, the temples, the back of the hand, and the forearm, where a weight of .002 gram ($\frac{1}{30}$ grain) can be perceived. The weight must be increased to .005 to .015 gram to be felt by the fingers, and to 1.0 gram when laid on the finger-nail.[1]

The power of discriminating differences of pressure applied to the skin is tested by finding the smallest increase that must be added to a weight in order that it may be perceived as being heavier. This increment is not, as might be supposed, the same for weights of different value, but it bears a distinct proportion to them. Thus, a weight of 11 grains may just be perceptibly heavier than one of 10 grains; but if we start with a weight of 100 grains, a single grain added to it will arouse no difference of sensation, an increment of 10 grains being necessary in order that one weight may appear heavier than the other. This fact is the basis for Weber's law of the relation between stimulus and sensation; this law may be formulated as follows: *The amount of stimulus necessary to provoke a perceptible increase of sensation always bears the same ratio to the amount of stimulus already applied.* This law is found to be only approximately correct, especially when very small and very large

[1] Aubert and Kammler: *Moleschott's Untersuchungen*, 1859, vol. v. p. 145.

weights are compared. Fechner attempted to express more exactly the relation between the intensity of stimulus and sensation in his "psycho-physical law," thus: *The intensity of sensation varies with the logarithm of the stimulus.* In other words, the sensation increases in arithmetical progression, while the stimulus increases in geometrical progression. With moderate weights a difference of pressure is perceptible when the ratio of increase is smaller than when either very small or very large weights are used; that is, sensitiveness to pressure-change is keenest under moderate stimulation.

It is said that the forehead, the lips, and the temples appreciate an increase of $\frac{1}{40}$ to $\frac{1}{30}$ of the weight estimated, while the skin of the head, the fingers, and the forearm requires an increase of $\frac{1}{20}$ to $\frac{1}{10}$ for its perception. In this as in other kinds of sensation it is the difference, or variation of intensity, of the sensation of which the mind takes particular cognizance. One touch-sensation is more acutely perceived when contrasted with another than when felt alone. Weber[1] found the discrimination of pressure-differences to be finer when two weights were laid in rapid succession on the same skin-area than when the weights were applied either simultaneously or successively to different parts. If a finger be dipped in a cup of mercury or of water having the same temperature as the skin, the pressure will be marked only at the margin between the air and the fluid, and if the finger be moved up and down it will seem as if a ring were being slid back and forth upon it. The fingers are particularly sensitive to intermittent variations of pressure—a facility the use of which is manifest when the function of these parts is considered.

Two weights, in being tested, should press upon equal areas of skin; according to Weber,[2] if two equal weights have different superficial expanse, that which touches the larger skin-surface, and thereby excites the greater number of touch-nerves, will appear to be the heavier. This result, however, cannot always, nor indeed usually, be verified. The simultaneous excitement of other sensations may modify that of pressure; thus, when two coins of equal weight, but one warm and the other cold, are laid upon the hand or the forehead, the cold one appears to be much the heavier.

There is a sensation of *after-pressure* depending for its strength on the amount of the weight and the length of time this weight has been applied. In fact, this after-sensation may produce a striking effect on consciousness, a familiar example of which is the persistence of the sense of pressure of the hat-band after the head-covering is removed. Even light weights leave an after-sensation, and, in order to be perceived as separate, must be applied at intervals of not less than $\frac{1}{480}$ to $\frac{1}{610}$ of a second. It is said that when the finger is applied to the rim of a rotating wheel provided with blunt teeth, the separate teeth are no longer felt, and the margin seems smooth, when the contacts succeed each other at the rate of 500 to 600 in a second.[3] Vibrations of

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[1] "Tastsinn und Gemeingefühl," *Wagner's Handwörterbuch der Physiologie*, 1846.

[2] Quoted in *Hermann's Handbuch der Physiologie*, Bd. iii. 2, S. 336.

[3] Landois and Stirling: *Human Physiology*, 1886.

a string cease to be appreciated by the finger when they have a rate of between 1500 and 1600 per second.

The Localization of Touch-sensation.—When a touch-sensation is felt, the mind inevitably refers the irritation to some particular part of the surface of the body, and the sensation seems to be localized in this area. On the accurate localization of tactile sensations depends not only the safety of the individual, but also the performance of the ordinary acts of life.

We may suppose that to each area of peripheral distribution of tactile nerve-fibres in the skin there corresponds an area of tactile nerve-cells in the brain. It can hardly be doubted that the nerve-cells are divided into physiological groups characterized by inherent and inborn quality-differences in the sensations aroused by their respective excitements. The reference of the sensations aroused by the excitement of definite nerve-cells to definite parts of the periphery is a power acquired through the physiological experiences of the earliest months of life. Through the sense of sight the seat of irritation is recognized, and through muscular sensation its relation to surrounding parts is experimentally explored, so that cumulative harmonious experiences of tactile, visual, and muscular sensations finally bring into correspondence the various areas with definite varieties of touch-sensation, or, to use an expression of Lotze's,[1] every area of the skin acquires a "local sign" by which it is distinguished in consciousness.

This power of localization differs widely for different parts of the skin. The fineness of the localizing sense for any skin-area is easily estimated by determining how far apart the tips of a pair of compasses, applied to the skin, must be separated in order to be felt as two. For this experiment the compass-points must be smooth, and they should not be applied heavily. The general result of such an inquiry is that the compass-points may be nearer together, and still be distinguished as two, in proportion as the surfaces to which they are applied have greater mobility. Since it is just such parts of the body as the tips of the tongue and the fingers that are chiefly used in determining the position of objects, the advantage of such an arrangement is obvious. The skin can thus be marked out in areas (*tactile areas*), within each of which the compass-points are felt as a single object, but if they are separated so as to fall beyond the borders of these areas, they are at once perceived to be two.

The following figures[2] represent the distances at which the compass-points can just be distinguished as double when applied to various parts of the body:

Tip of tongue	1.1 mm.
Palm of last phalanx of finger	2.2 "
Palm of second phalanx of finger	4.4 "
Tip of nose	6.6 "
Back of second phalanx of finger	11.1 "
Back of hand	29.8 "
Forearm	39.6 "
Sternum	44 "
Back	66 "

[1] Funke, in *Hermann's Handbuch der Physiologie*, Bd. iii. 2, S. 404.
[2] Foster's *Physiology*, 5th ed., 1891.

It will be observed that accuracy of localization and sensitiveness to pressure find their most perfect manifestations in widely separate regions of the skin.

Tactile areas are found to have a general oval form with the long axis parallel with the long axis of the member investigated. If the compass-points, separated, say, half an inch apart, be passed over the skin of the palm from the middle of the hand to the finger-tips, the sensation will be that of a single line gradually separating into two diverging lines. The result, of course, depends on the compass-points passing successively through areas of finer localization. If an area be marked out on a part of the skin where localization is poor, within which area two points simultaneously applied appear to be one, a single point moved within it is still perceived to change its place, and two points successively applied may be perceived to occupy different positions. The mental fusion or separation of the two compass-points cannot depend altogether on their being placed over the terminal twigs of the same or of two adjoining nerve-fibres, for, were this the case, the points could be discriminated when separated by a very small distance across the line drawn between the endings of adjoining nerve-fibres, while on either side the points would have to be much more widely separated in the area of distribution of a single fibre. The important factor in the mental separation of two stimulated points is, that between such points there shall be found a certain number of sensory elements which are unstimulated.[1] Practice in such experiments greatly increases the power to localize impressions. This improvement is evidently due not to the establishment of new nerves, but to a more perfect discrimination of sensations in the nerve-centres. When, by practice, the localizing power of the skin of a finger of one hand has been increased, it is found that the same improvement has been acquired by the corresponding, but untrained, finger of the other hand; in other words, the localizing power is central, not peripheral.

Pressure-points.—It has been found that if a light object, such as a lead-pencil, be allowed to rest by a narrow extremity successively on different parts of the skin, its weight will appear very different according to the part which is touched. If the spots on which the weight appears greatest be marked with ink, they will be found to have a constant position, and the skin may therefore be mapped out in areas of *pressure-points*, which are believed to indicate the place of ending of pressure-nerve filaments.

The Importance of the End-organ.—The sense of touch or pressure is a special sense; that is, any irritation conveyed to the nerve-centres in which the nerves of pressure terminate gives rise to a feeling of touch, just as disturbance in the visual or the auditory centre is recognized in consciousness as a sensation of sight or of sound. The complex anatomical structures known as *sense-organs* may be considered as instruments each of which is differentiated in a manner to make it particularly irritable toward some special form of energy. Thus, the retina is most sensitive to the luminiferous ether; the organ of Corti, to waves of endolymph, etc. To this differentiation of structure the

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[1] Weber: "Tastsinn und Gemeingefühl," *Wagner's Handwörterbuch der Physiologie*, 1846.

sensitiveness of the body to the forces of nature is chiefly due. The peripheral ending of the pressure nerve, whether a naked axis-cylinder or a touch-corpuscle, is no doubt modified to be particularly irritable toward that form of energy manifested in the molecular vibration of the tissue solids, brought about by contact with foreign objects. Hairs, particularly those in certain localities of some animals, as the whiskers of the cat, appear to have the function of transmitting mechanical vibrations to the nerve-endings in greater intensity than could be accomplished through the skin alone.

No true sense of touch is aroused by direct irritation of a nerve-trunk or exposed tissue, and touch-sensations do not arise from irritation of the internal surfaces of the body. A fluid of the temperature of the body gives, when swallowed, no sensation in the stomach; when cooler or warmer than the body, there is a sensation due, probably, to a transmission of temperature change to the skin of the abdomen.

Touch Illusions.—Certain peculiar errors in judgment may arise when tactile sensations are associated in a manner unusual in experience. Thus, in an experiment said to have been devised by Aristotle, if the forefinger and the middle finger be crossed, a marble rolled between their tips will appear to be two marbles; if the crossed finger-ends be applied to the tip of the nose, there seems to be two noses. The illusion is due to the fact that under ordinary circumstances simultaneous tactile sensations from the radial side of the forefinger and the ulnar side of the middle finger are always caused by two different objects. It is a not uncommon surgical operation to replace a loss of skin on the nose by cutting a flap in the skin of the forehead, without injury to the nerves, and sliding the flap round upon the nose. Touching the piece of transplanted skin gives the patient the sensation of being touched, not upon the nose, but upon the forehead; after a time, however, a new fund of experience is accumulated, and the sensation of contact with the transplanted flap is rightly referred to the nose. Persons who have suffered amputation of a lower limb often complain of cramps and other sensations in the lost toes. The illusion no doubt comes from irritation, in the nerve-stump, of fibres which previously bore irritations from the toes.

2. **Temperature Sense.**—The skin is also an organ for the detection of changes of temperature in the outer world. Such temperature differences probably make themselves manifest by raising or lowering the temperature of the skin itself, and thus in some way irritating the terminal parts of certain sensory nerves, the *temperature nerves*. The sensitiveness of the skin to temperature variations is not the same in all parts; thus, it is more acute in the skin of the face than in that of the hand; in the legs and the trunk the sensibility is least. We refer temperature sensations, somewhat like those of touch, to the periphery of the body, and localize them on the surface. The skin over various parts of the body may have different temperatures without exciting corresponding local differences of sensation. Thus, the forehead and the hand usually seem to be of the same temperature, but if the palm be laid upon the temples, there is commonly felt a decided sensation of temperature change in one or

both surfaces. As in other sensations, fatigue and contrast play an important part in the sense perceptions of temperature, and stimuli of rapidly-changing intensity provoke the strongest sensations; thus, when two fingers are both dipped into hot or cold water, the fluid seems hotter or colder to that finger which is alternately raised and lowered.

In changing to a place of different temperature the skin for a time seems warmer or cooler, but soon the temperature sensation declines, and on returning to the original temperature the reverse feeling of cold or of warmth is experienced. For every part of the skin, then, there is a degree of temperature, elevation above or depression below which arouses respectively the feeling of warmth or of cold, and the temperature of the skin determining the physiological null-point may vary within wide limits.

The smallest differences of temperature that can be perceived fall, for most parts of the skin, within 1° C. The skin of the temples gives perception of differences of 0.4°–0.3° C. The surface of the arm discriminates 0.2°; the hollow of the hand, 0.5°–0.4°; the middle of the back, 1.2°.[1]

The size of the sensory surface affected modifies the intensity of temperature sensation : if the whole of one hand and a single finger of the other hand be dipped into warm or cold water, the temperature will seem higher or lower to the member having the greatest surface immersed.

Cold and Warm Points.—The skin is not uniformly sensitive to temperature changes, but its appreciation of them seems to be limited to certain points distributed more or less thickly over the surface. These spots appear to be the places of termination of the temperature nerves in the epidermis (Fig. 288). There is little doubt that there are two distinct varieties of temperature nerves, one of which appreciates elevation of temperature, or heat, and the other diminution of temperature, or cold. Thus, if a blunt-pointed metal rod be warmed and be touched in succession to various parts of the skin, at certain spots it will be felt as very warm, while at others it will not seem warm at all. If, on the contrary, the rod be cooled, a series of *cold points* may in the same way be made out. The point of an ordinary lead-pencil may be used with some success to pick out the cold spots. The "cold points" are more numerous than the "hot," and those of each variety are more or less distinctly grouped round centres, as

Fig. 288.—Cutaneous "cold" spots (vertical shading) and "hot" spots (horizontal shading), anterior surface of the thigh (from Waller, after Goldscheider).

would be expected from the manner of nerve-distribution, though the groups overlap to some extent (Fig. 288). Certain substances appear to act, probably by chemical means, as specific excitants of the two sets of nerves. Thus, menthol applied to the skin gives a sensation of cold, while an atmo-

[1] Nothnagel: *Deutsche Archiv für klinische Medicin,* 1866, ii. S. 284.

sphere of carbon dioxide surrounding an area of skin gives a sensation of warmth.[1]

The specific difference of the two sets of temperature nerves is indicated by the fact that when a warm and a cold body held close together are simultaneously brought near the skin, the sensation is either one of both warmth and cold, or now one and now the other sensation predominates.[2] Any stimulation, whether mechanical or electrical, applied to the sensitive points thus far described in the skin, for the appreciation of either pressure, heat, or cold, provokes, when effective, only the proper sensation of that point; any irritation of a cold, hot, or pressure point gives rise, respectively, to the sensation of cold, heat, or pressure alone.

As in other organs of special sense, the peripheral terminations of the temperature nerves seem modified to be especially irritable toward their appropriate form of physical stimulus. Cold or heat directly applied to the nerve-trunk excites no temperature sensation. Thus, if the elbow be dipped into a freezing mixture, as the lowered temperature penetrates to the ulnar nerve the sensation will be one, not of cold, but of dull pain, and it will be referred to the hand and the fingers. The internal mucous surfaces of the body, from the œsophagus to the rectum, inclusive, have no power of discriminating temperature sensations; a clyster of water cooled to from 7° to 16° C., if not held too long, is only perceived as cold when the water escapes through the skin of the anus.

The doctrine of *specific nerve energy,* enunciated by E. H. Weber, was intended to convey the idea elaborated above, that each nerve of special sense, however irritated, gives rise to its own peculiar quality of sensation. But it seems clear that the existence and quality of the sensation are, respectively, properties of the activity, not of the nerve-fibre, but of the peripheral end-organ and the nerve-centres.

3. **Common Sensation and Pain.**—The sensations thus far considered have been called *special sensations,* because each affects the consciousness in quite a different way, and any irritation which excites the sense apparatus provokes a sensation of definite quality and measurable intensity.

Pain is a sensation which, according to common but erroneous belief, is the result of sufficiently intensifying any of the simple sensations.

Pains have received various names to distinguish their quality, according to the mode in which experience shows they may have been produced, as cutting, tearing, burning, grinding, etc. One peculiar mark that distinguishes painful sensations is the lack of complete localization. While lesser pains are referred with fair exactness to different parts of the body, and even to those internal parts devoid of tactile sensibility, greater pains radiate and seem diffused over neighboring parts. Pain also differs from special sensation in the long latent

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[1] Goldscheider: *Du Bois-Reymond's Archiv für Physiologie,* 1886, 1887; Blix: *Zeitschrift für Biologie,* 1884; Donaldson: *Mind,* vol. 39, 1885.

[2] Czermak: *Sitzungsberichte d. Wiener Akad.,* 1855, p. 500; Klug: *Arb. d. physiol. Anstalt zu Leipzig,* 1876, p. 168.

period preceding its development. The evidence of physiological experiment is against the belief that any irritation of the nerves of so-called "special senses" can produce pains, but it teaches that this sensation is the result of the excessive or unnatural stimulation of a group of nerves whose function is to give rise to what is indefinitely called "common sensation." By this term is designated that consciousness which we more or less definitely have, at any moment, of the condition and position of the various parts of our bodies. When tactile, temperature, and visual sensations are eliminated, we are still able to designate with considerable accuracy the position of our limbs, and we become aware with extraordinary exactness of any change in that position, indicating the possession of a *posture sense.* The nerves of common sensation must, then, be continuously active in carrying to the sensorium impulses which, though they do not excite distinct consciousness, probably are of the utmost importance in keeping the nerve-centres informed of the relative positions and physiological condition of the various parts of the organism, and it is not improbable that they are the afferent channels for many reflex acts which tend to preserve the equilibrium of the body. The sudden failure of these sensations in a part of the body would probably be felt as acutely as the silence which succeeds a loud noise to which the ear has become accustomed. Pain is thought to be the result of excessive stimulation of the nerves of common sensation, though it must be admitted that we know next to nothing of the anatomical and physiological conditions on which this sensation is dependent. It is said not only that most internal organs possess no definite tactile or thermal sensibility, but that, when normal, such irritation as is caused by cutting, burning, and pinching seems to cause no pain;[1] let them, however, become inflamed, and their sensitiveness to pain is sufficiently acute. The facts of labor-pains, of colic, and other visceral disturbances which are attended by no inflammatory condition show, however, that the factors on which the existence of pain depends are not as yet fully understood.

The physiological facts on which is based the belief in "common sensation" are indisputable, but the evidence for a special nervous apparatus for such sensibility is based rather on exclusion of known nerve-organs than on positive demonstration. In the category of common sensations have been included also such feelings as "tickling," shivering, hunger, thirst, and sexual sensations. The feeling of fatigue which follows either muscular or mental exertion may be placed in the same group.

A general feature of common sensations is their subjective character; they are not definitely localized within the body, nor are they projected external to it, as in the case of the "special senses."

Between the common sensation and its existing cause there is no measurable proportion, as is found, for instance, in the study of the pressure sense. It may be stated that pressure and temperature sensations were within a recent period grouped among common sensations, and future investigations may pos-

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[1] Foster's *Physiology*, 1891, p. 1420.

sibly limit each of the feelings now classed together as "common sensations" to definite anatomical structures.

When the punctiform distribution of various sensations in the skin is investigated, some points are found in which no other sensation than that of pain can be excited, and it has been thought that such spots mark the place of ending of nerves of common sensibility.

Transferred or "Sympathetic" Pains; Allochiria.—It has long been a matter of clinical observation that disease seated in certain internal organs is often accompanied by superficial pain and tenderness in widely removed parts of the body; for example, a decayed tooth frequently causes intense pain in the ear; disease of heart or of aorta may cause pain between the shoulders, etc. The subject has received most accurate investigation from Head,[1] who has shown that there is an intimate nervous connection between the internal organs and definite areas of the skin, manifested by pain and tenderness appearing in sharply-localized regions on the surface when definite organs become disordered. He has also demonstrated that disorders of the thoracic and abdominal viscera not only produce pain and tenderness on the surface of the body, but also cause pain and tenderness over certain areas of the scalp. Head is inclined to explain the topographical association of skin-tenderness with visceral disorders by the assumption that the nerve-supplies of the parts so related find their origin within the same segment of the spinal cord. The sensory result of visceral irritation may be summarized in the following way: "When a painful stimulus is applied to a part of low sensibility in *close central connection* with a part of much greater sensibility, the pain produced is felt in the part of higher sensibility rather than in the part of lower sensibility to which the stimulus was actually applied."

That this transferred localization may characterize other sensations than those of pain has been definitely observed by Obersteiner,[2] who found that in patients suffering from certain central nervous lesions tactile irritation of a certain point on the skin was referred by them to some other part of the body, usually the corresponding point on the other side. He designated this transference of sensation by the term *allochiria*, meaning a confusion of sides.

4. **Muscular Sensation.**—Closely allied to common sensation, if not a part of it, is *muscular sensation*. If two weights are to be compared, we naturally do not lay them on the skin to determine their pressure-difference, but we lift and weigh them in the hands, and experience shows that a much more accurate estimate may thus be made.

We undoubtedly have a keen perception of the tension of a muscle, and therefore of the amount of resistance against which it is contracting. This perception may be the outcome of a direct consciousness of the amount of motor energy sent out from the motor cells, or it may be due to the inflow of sensory impulses which show the tension to which the muscles have been subjected. The latter view has more to be said in its favor. The sensory nerves involved in this process are probably distributed rather to the tendons in which the mus-

1 *Brain*, 1893-94.   2 *Ibid.*, 1881.

cles terminate than to the muscular substance itself. There is reason to believe that the joints are particularly rich in such a nerve-supply. Golgi[1] has described two distinct modes of nerve-ending in tendon and at the line of division between muscle and tendon ; and Sherrington[2] has shown terminal sensory fibres to be enclosed in peculiar isolated groups of muscle-fibres, the " muscle spindles," found at the origin of tendons. According to the latter author, from one-third to one-half of all the spinal-nerve fibres found in muscle are sensory in function.

When we consider that it is through muscular sensation that we derive our most accurate conceptions of the form, weight, and position of objects, and through which we explore our own body-surface and distinguish its areas of localization ; that this is the fundamental sense by which the sensations arising in most other organs are tested and verified ; and that it is from the sense of muscular movement that we can form ideas of time and space,—it may well be regarded as the mother of all sense-perceptions. Normal muscles, even when functionally inactive, are still in a state of tonic contraction ; it is not improbable that this tone is a reflex action whose sensory element is formed by the impulses travelling along nerves of muscular sensation. Such impulses are probably indispensable to the preservation of the equilibrium of the body.

The clinical study of disease in the central nervous system affords strong evidence of the functional independence of the sense organs involved in the appreciation of touch, heat, cold, and pain. In certain diseases of the spinal cord, areas of skin may be mapped out in which sensations of pressure are lost, but those of temperature remain, and *vice versâ.* In other diseases the patient can appreciate warmth applied to the skin, but not cold.

The sensations of cold and pressure seem to be usually lost or retained together, while those of warmth and pain have a similar connection. It is a peculiar fact that sometimes in the early stages of ether and chloroform narcosis the sense of touch remains while that of pain is abolished. Funke[3] refers to two cases in which, while the tactile sense was preserved, muscular sensation was lost, and an object could be held in the grasp only while the eyes were turned upon it:

Hunger and Thirst.—Hunger and thirst are peculiar sensations which depend partly on local and partly on general causes. Diminution in the bulk of water and of circulating aliment in the body no doubt causes excitement of sensory nerves on which depend the feelings of thirst and hunger, but in ordinary life these feelings are dependent on the physical condition of certain mucous surfaces. Any circumstance which causes drying of the lining membrane of the mouth provokes thirst, and some condition of the empty stomach arouses hunger. Thirst may be assuaged by introducing water directly into the stomach through a gastric fistula, though to effect the purpose a larger quantity must be employed in this way than by the mouth. Hunger in a

[1] *Hofmann und Schwalbe's Jahresbericht,* Abth. I. Bd. vii. S. 93.
[2] *Journal of Physiology,* vol. xvii. p. 211.
[3] " Der Tastsinn," *Hermann's Handbuch der Physiologie,* Bd. iii. S. 2.

somewhat similar manner may be appeased by rectal alimentation. It seems probable, however, that these sensations as usually felt are the result of a sort of habit, depending on the physiological condition of the secreting and absorbing mechanisms of the alimentary canal.

Clinical observation has shown that " bulimia," or voracious appetite, is frequently a result of disease in certain parts of the central nervous system. We are therefore justified in speaking of a " hunger-centre."[1]

E. The Equilibrium of the Body; the Function of the Semicircular Canals.

The term *equilibrium*, as applied to the condition of the body, whether at rest or in motion, indicates a state in which all the skeletal muscles are under control of nerve-centres, so that they combine, when required, to resist the effect of gravity or to execute some co-ordinated motion. The preservation of equilibrium is manifestly of fundamental importance in animal life, and we find, accordingly, several mechanisms sharing in this function. That the motor co-ordinating centres may act properly, they must receive sensory impressions conveying information of the relative position of the body at any given moment. The sum-total of these sensations may be characterized as the *sense of equilibrium*, and it is probably not going too far to assume that every known sensation contributes to this fund of information. Thus, in ordinary life the position of objects is commonly determined by the sense of sight : when one tries to walk while looking through a prism, objects are not properly localized by vision, and improper co-ordination results. The contact of the soles of the feet with the ground, and that of the surface of the body with various objects, are common sources of information as to our relation with the environment. Standing upright, and still more when in motion, the muscular sense is active in appreciating the tension, active or passive, of the muscles. In the erect position, with eyes closed, a writing point attached to the head will show that the body sways in a peculiar manner indicating successive contraction of different groups of muscles ; and a person with failure of muscular and tactile sensibility, as in locomotor ataxy, cannot stand with eyes closed, and his movements, even when sight is employed, are exaggerated and unnatural. Attention has previously been called to the fact that air-waves, irrespective of those producing sound-sensations, exert an influence upon the tympanic membrane by which we are capable of appreciating the presence and, to some extent, the physical character of objects. Whether this sensation involves the nerves of touch, those of common sensibility, or those distributed to the internal ear, is uncertain.

In the absence of any of these sensations the loss may be made up by more perfect development of others. Ordinarily, the sensory information from all these sources, when compared in consciousness, harmonizes and gives rise to a concrete idea of position. Frequently, however, one of the sources of sense-impression suddenly fails us or its testimony conflicts with that of other sense

[1] Ewald: *Diseases of the Stomach*, p. 397.

organs; the result is disturbance of equilibrium. A very common outcome of this conflict of sensations is *dizziness* or *nausea.* The distress arising from wearing ill-fitting glasses and the sensations experienced when one looks down from a high eminence are examples in point. Internal disorders exciting nerves of common sensation have the same effect, though the relation borne by visceral sensations to equilibrium is very ill known. A false idea of position of the body, a sense of falling in one direction or another, may lead to sudden effort of recovery by which the person is precipitated to the opposite side. Thus, when looking at rapidly-moving water erroneous ideas of equilibrium are gained through the visual sense, and there is a strong tendency for the body to precipitate itself in one direction or another. When, in going up a stair-case, one miscalculates the number of steps, a peculiar sensation of want of equilibrium is aroused through the muscular sense. It is clear, then, that the sense of equilibrium is served by various sense organs, and a complete discussion of this function would entail a consideration of the whole field of nerve-muscle physiology. There is, however, good reason for believing that there is a special sense organ for determining the position and direction of movement of the head and, by inference, of the whole body. The terminal organ of this sense apparatus of equilibrium is found in the system of semicircular canals of the internal ear.

Experiments on the lower animals, chiefly performed on birds, show a constant motor disturbance to follow division of any or all of the semicircular canals. These disturbances are of two kinds. When the animal is at rest it does not stand in a natural fashion, but *sprawls* in a more or less exaggerated degree. It holds its head in an unnatural position, as with the vertex touching the back, or with the beak turned down toward the legs or bent over to one side. Immediately after the operation, and whenever it is disturbed, the animal goes through peculiar *forced* movements, together with rolling or twitching of the eyes, of various kinds and degrees of violence, depending on the position and number of canals severed. The disturbance varies from simple unsteadiness in gait, with swaying motions of the head, to complete lack of co-ordination and a violence of movement almost comparable to that of a chicken whose head has been cut off. Essentially the same results have been determined to follow injury of the semicircular canals of widely different groups of animals.

These results have been explained by the assumption that the hair-cells on the *cristæ acusticæ* of the ampullæ of the semicircular canals are irritated by increase or decrease of pressure of the endolymph upon them, and thus give rise to sensory impressions from which ideas of change of position are derived. Section of the canal, by draining off the endolymph, would cause abnormal pressure-irritation. The anatomical relations of the semicircular canals afford an obvious basis for this view, for the canals of each ear are almost exactly at right angles to one another, occupying the three planes of space; considering the two ears, the horizontal canals are nearly in the same plane, and the anterior vertical canal of one side is nearly parallel with the posterior vertical canal

of the other side.   Any possible movement of the head would thus produce an increase of endolymph-pressure upon the hair-cells in one ampulla and a decrease of pressure in the ampulla of the parallel canal, and every change of position would be accompanied by the irritation of definite ampullæ with definite degrees of excitement (Fig. 289).   Experiments on man afford considerable support to this theory of the function of the semicircular canals.   A person with eyes closed and with muscular and tactile sensations eliminated, supported on a table which can be rotated in all directions, can determine with considerable accuracy not only that he is moved, but in what direction and, to some extent, through how great an angle.   Further, when brought to rest after a series of rotations the person under observation feels a sensation of motion in the opposite direction.   Each of these results should be expected to follow were the

FIG. 289. — Diagrammatic horizontal section through the head to illustrate the planes occupied by the semicircular canals (after Waller): s, superior canal; P, posterior canal; H, horizontal canal.

theory in question correct.   The observations of James have shown that with deaf mutes in whom the internal ear was at fault rapid rotation in an ordinary "swing" failed to produce the dizziness which is the common effect in ordinary individuals.   On the other hand, diseases which may be supposed to alter the intra-labyrinthine pressure are characterized by the symptoms of vertigo and inco-ordination of movement.   The presumable effect of cutting the semicircular canals is that the escape of endolymph changes the pressure upon the sensory hair-cells and gives the animal the sensation of falling in one direction or another, so that he is impelled to make compensatory or *forced* movements to counteract this imaginary change of position.   In birds and in fishes, whose life is passed more or less exclusively in a medium in which tactile and muscular sensation can contribute little to the sense of equilibrium, the semicircular canals are especially well developed.[1]   In fishes, though section of the canals themselves produces no disturbance, division of the nerves supplying the ampullæ usually gives rise to marked forced movements, as shown in somersaults, spiral swimming, etc. when set free in the water.   When, however the nerves are cut with great care, with sharp scissors, so as to avoid traction on or crushing of the nerves, such forced movements do not follow.   The movements in this case, then, as in that of the pigeon, are the outcome of direct irritation of the equilibrium mechanism, and, according to our present conception of the function of the semicircular canals in its relation to equilibrium, we must regard it as a terminal organ which is exceedingly sensitive to such mechanical irritations as may arise from variations of endolymph-pressure upon the ampullary hair-cells, but which may be destroyed without causing inco-ordination of movement, and which may therefore more or less completely be substituted in function by other sense organs.

[1] Sewall: *Journal of Physiology*, 1884, iv. p. 339.

According to Lee[1] and others, the equilibrium of rest and motion, or static and dynamic equilibrium, depends upon the irritation of different nerve-terminals. The manner of action of the latter has been considered. As to the nervous mechanism on which *static* equilibrium depends, Lee is of the opinion that the knowledge of the position of the head while at rest comes from the relation of the otoliths in the vestibular sacs to the nerve-endings on the *maculæ acusticæ.* These otoliths form considerable masses in the ears of fishes, and the intensity and direction of their pressure upon hair-cells must vary with the spatial relations of the head, and thus be comparable, in the sense of position which they arouse, to the tactile sensations derived from the soles of the feet in man.

F. Smell.

The complex paired cavity of the nose is divisible into a lower respiratory and an upper olfactory tract, the mucous membrane over each of which is distinctive. The covering of the respiratory tract is known as the *Schneiderian* or *pituitary* membrane; its surface is overlaid with cylindrical ciliated epithelium, the ciliary current of which is directed posteriorly toward the pharynx.

The Schneiderian membrane lines the lower two-thirds of the septum, the middle and inferior turbinated bodies, and the bony sinuses which communicate with the nasal chamber. The membrane upon the turbinated bodies and the lower part of the septum is composed largely of erectile tissue.

The function of the respiratory tract is threefold : it restrains the passage of solid particles into the lungs; it warms the air inspired to approximately
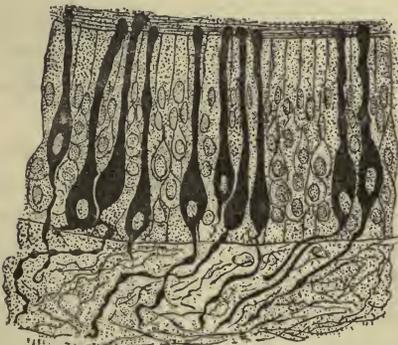
FIG. 290.—Section of olfactory mucous membrane (after V. Brunn): the olfactory cells are in black.
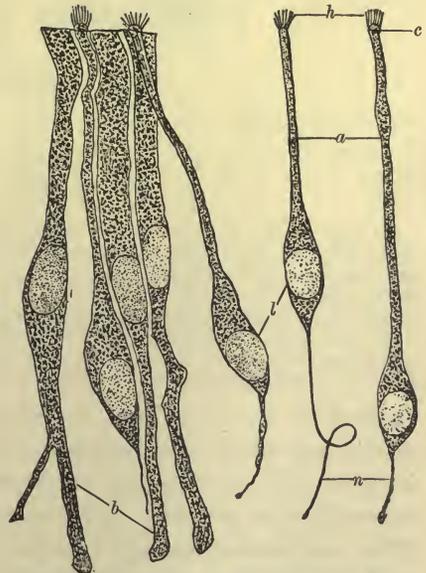
FIG. 291.—Cells of the olfactory region (after V. Brunn): *a*, olfactory cells; *b*, epithelial cells; *n*, central process prolonged as an olfactory nerve-fibril; *l*, nucleus; *c*, knob-like clear termination of peripheral process; *h*, bunch of olfactory hairs.

the temperature of the body; and it gives up moisture sufficient nearly to saturate the air.

[1] *Journal of Physiology,* xv. p. 311; xvii. p. 192.

The olfactory mucous membrane, which alone is the peripheral organ for smell, is seated in the upper part of the nasal chamber, away from the line of the direct current of inspired air. The membrane is thick and is covered by an epithelium composed of two kinds of cells, columnar and rod cells. The latter are the true *olfactory cells* (Figs. 290, 291), with which the fibres of the olfactory nerve are known to be connected. These olfactory cells, in fact, are comparable to nerve-cells in that the fibres connected with them, the fibres composing the olfactory nerve, are direct outgrowths from the cells (Fig. 292), essentially similar in every way to the nerve-fibre processes springing from nerve-cells in the nerve-centres. In this respect the olfactory cells differ from the sensory cells in other organs of special sense. The membrane
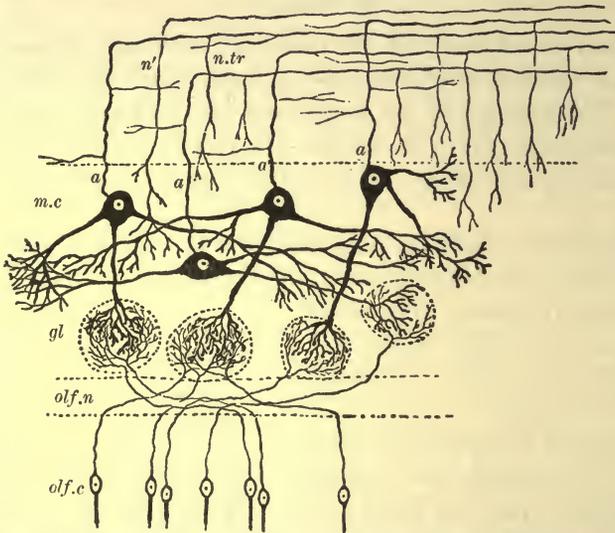
Fig. 292.—Diagram of the connections of cells and fibres in the olfactory bulb (Schäfer, in Quain's *Anatomy*): *olf.c*, cells of the olfactory mucous membrane; *olf.n*, deepest layer of the bulb, composed of the olfactory nerve-fibres which are prolonged from the olfactory cells; *gl*, olfactory glomeruli, containing arborization of the olfactory nerve-fibres and of the dendrons of the mitral cells; *m.c*, mitral cells; *a*, thin axis-cylinder process passing toward the nerve-fibre layer, *n.tr*, of the bulb to become continuous with fibres of the olfactory tract; these axis-cylinder processes are seen to give off collaterals, some of which pass again into the deeper layers of the bulb; *n'*, a nerve-fibre from the olfactory tract ramifying in the gray matter of the bulb.

appears to be not ciliated except near its juncture with the Schneiderian membrane, where the columnar cells acquire cilia and gradually pass over into the cells covering the respiratory tract. Substances exciting the sense of smell exist as gases or in a fine state of division in the air inspired. They reach the olfactory mucous membrane by diffusion, assisted by the modified inspiratory movements of "sniffing" and "smelling," and are most acutely perceived when the air containing them is warmed to the body-temperature. The amount of odoriferous matter that may thus be recognized is extraordinarily small; thus, it is said that in one liter of air the odor of 0.000,005 gram of musk and of 0.000,000,005 gram of oil of peppermint can be perceived.[1] The odoriferous particles probably excite the

[1] Passy : *Comptes-rendus de la Société de Biologie*, 1892, p. 84.

sense of smell by coming into contact with the olfactory epithelium after solu-
tion in the layer of moisture covering it. This epithelium is easily thrown
out of function, as the common loss of smell when there is a "cold in the
head" testifies. When the nostril is filled with water in which an odorous
substance is dissolved, no sensation of smell is excited, but it is said that if
normal salt-solution, which injures the living tissues less than water, be used
as the solvent, the odor can still be perceived. In many lower animals the
sense of smell has an acuteness and an importance in their economy unknown
in the human race. It is probable that not only do different races have their
distinctive odors, but that each individual exhales an odor peculiar to himself,
distinguishable by the olfactory organs of certain animals. The classification
of odors is not very definite, and the relation of odors to one another in the
way of contrast and harmony is ill understood. No limited number of pri-
mary sensations, as in vision, have been discovered out of which other sen-
sations can be composed. Certain sensations, as those due to the inhalation
of ammonia and other irritant gases, are thought to be due to excitement of
the nasal filaments of the fifth nerve, and not of the olfactory.

Subjective sensations of smell are sometimes experienced, the result of some
irritation arising in the olfactory apparatus itself.

Finally, in man sensations of smell have their most important uses in con-
nection with taste; many so-called "tastes" owe their character wholly or
partly to the unconscious excitement of the sense of smell.

G. Taste.

The peripheral surfaces concerned in taste include, in variable degree, the
upper surface and sides of the tongue and the anterior surfaces of the soft
palate and of the anterior pillars of the fauces. Other parts of the buccal
and pharyngeal cavities are, in most persons, devoid of taste.[1]

The chief peripheral sensory organs of taste are groups of modified epi-
thelial cells, known as *taste-buds* (Fig. 293), seated in certain papillæ of the
tasting surfaces. According to some authors, only parts provided with taste-
buds can give taste-sensations.[2]

The structure of taste-buds is most easily studied in the *papilla foliata* of
the rabbit, a patch of fine, parallel wrinkles found on each side of the
back part of the tongue of the animal. The taste-bud is a somewhat globular
body seated in the folds of mucous membrane between the furrows of the
papilla. It is made up of a sheath of flattened, fusiform cells enclosing a
number of rod-like cells each of which terminates in a hair-like process. These
cells surround a central pore which opens into a furrow of the papilla.
The hair-bearing cells recall the appearance of the olfactory rod-cells, and
are probably the true sensory cells of taste, since between them terminate the
filaments of the gustatory nerve. In the human tongue taste-buds are con-

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[1] V. Vintschgau: "Geruchsinn," *Hermann's Handbuch der Physiologie*, iii. 2, 1880.
[2] Camerer: *Zeitschrift für Biologie*, 1870, vi. S. 440; Wilczynsky: *Hofmann und Schwalbe's Jahresbericht der Physiol.*, 1875.

fined to the fungiform papillæ, seen often as red dots scattered over the upper surface; to the circumvallate papillæ, the pores of the buds opening into the groove around the papilla; and to an area just in front of the anterior pillar of the fauces, which somewhat resembles the papilla foliata of the rabbit.

The sensory nerves distributed to the tongue include filaments from the glosso-pharyngeal, the lingual branch of the fifth, and the chorda tympani. The relation of these nerves to the sense of taste has been the occasion of much dispute. The weight of evidence probably favors the belief that the glosso-pharyngeal is the nerve of taste for the posterior third of the tongue, while the lingual and, to some extent, the chorda carry taste-impressions from the anterior two-thirds. Clinical cases have been cited to show that all the gustatory fibres arise from the brain as part of the glosso-pharyngeal nerve, whatever may be their subsequent course to the tongue. On the contrary, other cases have shown a marked loss of taste-sensation following upon lesions of the fifth nerve at or near its origin from the brain, while still others indicate that some of the taste-fibres may arise in the seventh nerve. The point is of practical importance in diagnosis, in the interpretation of loss of taste over any given part of the tongue, but the contradiction in the clinical cases reported has led to the general belief that the origin and course of the gustatory fibres are subject to considerable individual variations.
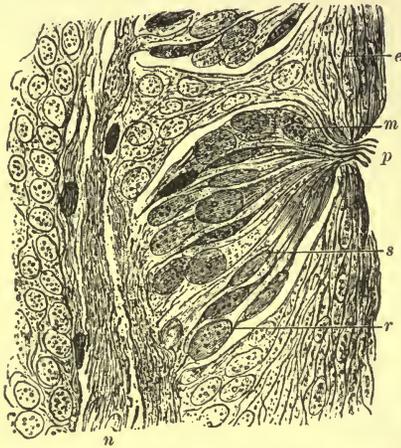
FIG. 293.—Section through one of the taste-buds of the papilla foliata of the rabbit (from Quain, after Ranvier), highly magnified: *p*, gustatory pore; *s*, gustatory cell; *r*, sustentacular cell; *m*, leucocyte containing granules; *e*, superficial epithelial cells; *n*, nerve-fibres.

Our taste-perceptions are ordinarily much modified by simultaneous olfactory sensations, as may easily be demonstrated by the difficulty experienced in distinguishing by taste an apple, an onion, and a potato, when the nostrils are closed. Sight has also an important influence, at least in quickening the expectancy for individual flavors. Every smoker knows the blunting of his perception for burning tobacco while in the dark; various dishes having distinctive flavors are said to lose much of their gustatory characteristics when the eyes are bandaged.

The intensity of gustatory sensation increases with the area to which the tasted substance is applied. The movements of mastication are peculiarly adapted to bring out the full taste value of substances taken into the mouth, and the act of swallowing, by which the morsel is rubbed between the tongue and the palate, has been proved to develop tastes not appreciable by simple contact with the sensory surface. A considerable area in the mid-dorsum of the tongue is said to be devoid of all taste-sensibility.[1]

[1] Shore: *Journal of Physiology*, 1892, vol. xiii. p. 191.

The sensitiveness of taste-sensation is greatest when the exciting substance is at the temperature of the body. Weber[1] found that when the tongue was dipped during one-half to one minute in water either at the freezing temperature or warmed to 50° C., the sweet taste of sugar could no longer be appreciated by it. It is probable that sapid substances reach the sensory endings of the nerves of taste only after being dissolved in the natural fluids of the mouth, and any artificial drying of the buccal surfaces or alteration of their secretion must affect taste-perceptions.

The excitement of the taste-nerves appears to depend not so much on the absolute amount of the substance to be detected as on the concentration of the

Auditory.   *Gustatory.*   *Tactile.*
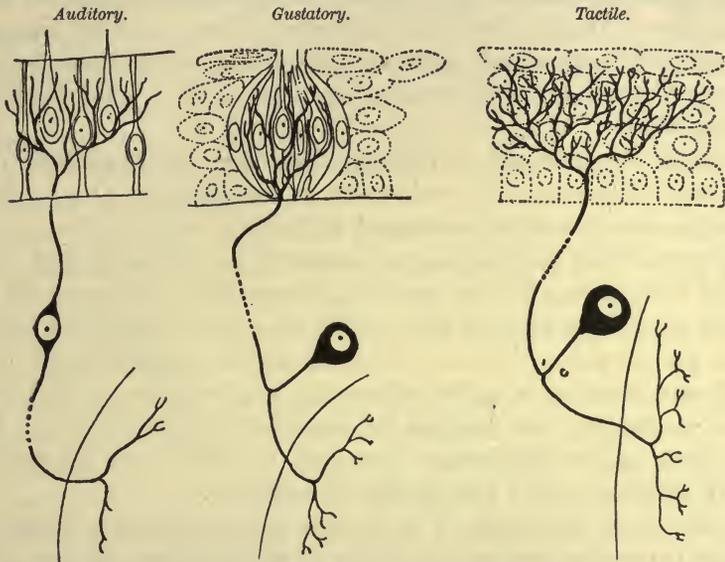
FIG. 294.—Diagram showing the mode of termination of sensory nerve-fibres in the auditory, gustatory, and tactile structures of vertebrata (from Quain, after Retzius). Each sense organ may be considered as essentially constructed of a nerve-cell with two processes, one finding its way centrally to cluster round other nerve-cells or their processes, and the other to terminate in the periphery. In the organ of smell the peripheral process is very short and is directly irritated by foreign particles, the original nerve-cell being represented by the olfactory cell (Fig. 291). In the organs of touch the nerve-cell is found in the ganglion of the posterior spinal nerve-root; the peripheral process is very long and is acted on indirectly through the modified epithelium round which it clusters. The same may be said of the other sense organs. See Quain's *Anatomy*, 10th ed., vol. iii. pt. 3, p. 152.

solution containing it. Thus, when 1 part of common salt to 213 of water was tasted by Valentin,[2] $1\frac{1}{2}$ cubic centimeters of the fluid was sufficient to give a saltish taste; when diluted so that the ratio of salt to water was 1 to 426, 12 cubic centimeters taken in the mouth scarcely gave the salt taste. Sulphate of quinine dissolved in the proportion 1 to 33,000 gave a decided bitter taste, but a solution 1 to 1,000,000 was with difficulty perceived as bitter.

It has generally been conceded that all gustatory sensations may be built up out of four *primary taste-sensations*—namely, *bitter, sweet, sour,* and *salt.* Some authors even limit the list to tastes of bitter and sweet (V. Vintschgau).

[1] *Archiv für Anatomie und Physiologie*, 1847, S. 342.   [2] *Lehrbuch der Physiologie*, 1848.

There is strong reason to believe that corresponding to the four primary taste-sensations there are separate centres and nerve-fibres, each of which, when excited, gives rise only to its appropriate taste-sensation. Substances which arouse the sense of taste are not appreciated in uniform degree over the surface of the tongue. Thus, to V. Vintschgau, at the tip of the tongue acids were perceived acutely, sweets somewhat less plainly, and bitter substances hardly at all. It is generally admitted that sweet and sour tastes are recognized chiefly at the front, and bitter, together with alkaline tastes, by the posterior part of the tongue. Strong evidence in favor of the specific difference between various taste-nerves is found in the fact that the same substance may excite a different gustatory sensation according as it is applied to the front or the back of the tongue. Thus, it has been demonstrated that a certain compound of saccharin (para-brom-benzoic sulphinide) appears to most persons to be sweet when applied to the tip of the tongue, but bitter in the region of the circumvallate papillæ.[1]

Oehrwall[2] has examined the different fungiform papillæ scattered over the tongue with reference to their sensitiveness to taste-stimuli. One hundred and twenty-five separate papillæ were tested with succinic acid, quinine, and sugar. Twenty-seven of the papillæ gave no response at all, indicating that they were devoid of taste-fibres. Of the remaining ninety-eight, twelve reacted to succinic acid alone, three to sugar alone, while none were found which were acted upon by quinine alone. The fact that some papillæ responded with only one form of taste-sensation is again evidence in favor of the view that there are separate nerve-fibres and endings for each fundamental sensation; but the figures given in the experiments show that the majority of the papillæ are provided with more than one variety of taste-fibre.

An extract of the leaves of a tropical plant, *Gymnema silvestre,* when applied to the tongue, renders it incapable of distinguishing the taste of sweet and bitter substances; it probably paralyzes the nerves of sweet and bitter sensations. When a solution of cocaine in sufficient strength is painted on the tongue, the various sensations from this member are said to be abolished in the following order: (1) General feeling and pain; (2) bitter taste; (3) sweet taste; (4) salt taste; (5) acid taste; (6) tactile perception (Shore).

That there are laws of contrast in taste-sensation has long been empirically known. Thus, the taste of cheese enhances the flavor of wine, but sweets impair it (Joh. Müller). It is unfortunate, from a hygienic standpoint at least, that in this most important department of the physiology of sensation investigations are almost wholly wanting.

Certain tastes may disguise others without physically neutralizing them; when, for example, sugar is mixed with vinegar, the overcoming of the acid taste is probably effected in the central nerve-organ.[3]

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[1] Howell and Kastle: *Studies from the Biological Laboratory of Johns Hopkins University.* 1887, iv. 13.

[2] *Skandinavisches Archiv für Physiologie,* 1890, vol. ii. p. 1.

[3] Brucke: *Vorlesungen über Physiologie,* 1876.

XII. PHYSIOLOGY OF SPECIAL MUSCULAR MECHANISMS.

A. The Action of Locomotor Mechanisms.

The Articulations.—The form, posture, and movements of vertebrates are largely determined by the structure of the skeleton and the method of union of the bones of which it is composed. There are two hundred bones in the human skeleton, and they are so connected together as to be immovable, or to allow of many varieties and degrees of motion. There are four principal methods of articulation:

1. **Union by Bony Substance (Sutures).**—This form of union occurs between the bones of the skull. These bones, which at birth are independent structures connected by fibrous tissue, gradually grow together and make a continuous whole, only a more or less distinct seam remaining as witness of the original condition.

2. **Union by Fibro-Cartilages (Symphyses).**—The bodies of the vertebræ and the pelvic bones are closely bound together by disks of fibro-cartilage. This material, which is very strong, but yielding and elastic, permits of a slight amount of movement when the force applied is considerable, and restores the bones to their original position on the removal of the force. The intervertebral disks act, moreover, as elastic cushions or buffers to deaden the effect of sudden jars.

3. **Union of Fibrous Bands (Syndesmoses).**—Some of the bones, as of the carpus and tarsus, are connected by interosseous ligaments which, at the same time that they bind the bones together, admit of a certain amount of play, the extent of the movement varying with the character of the surfaces and the length of the ligaments.

4. **Union by Joints.**—The adjacent surfaces of most of the bones are so formed as to permit of close contact and freedom of movement in special directions. The parts of the bones entering into the joint are clothed with very smooth cartilage, and the joint-surfaces are lubricated by synovial fluid, a viscid liquid secreted by a delicate membrane which lines the fibrous capsule by which the joint is surrounded. The joint-capsule is firmly attached to the bones at the margin of the articular cartilages, and, at the same time that it completely surrounds and isolates the joint-cavity, helps to bind the bones together. The bones are further united by strong ligaments, in some cases within and in other cases without the capsule. These ligaments are so placed that they are relaxed in certain positions of the joints and tightened in others;

they guide and limit the movements of the joints. The joint-surfaces always touch, although in some joints the parts in contact change with the position of the joint. If continuous contact of the joint-surfaces is to be maintained and free movement is to take place in special directions, it is evident that the opposing surfaces must not only be so constructed that they shall fit each other with great accuracy, but also have forms especially adapted to the movements peculiar to each of the joints.

The different joints exhibit a great variety of movements and may be classified as follows: gliding joints, hinge joints, condyloid joints, saddle joints, ball-and-socket joints, pivot joints. For a description of the structure and the peculiarities of these joints the student is referred to works on anatomy.[1] The contact of the surfaces of the joint is secured in part by the fibrous capsule, in part by the joint ligaments, and in part by the tension of the muscles. The elastic muscles are attached under slight tension, and, moreover, during waking hours are kept slightly contracted by tonus impulses of reflex origin. Another less evident but no less important condition is the atmospheric pressure. The capsule fits the joint closely and all the space within not occupied by the bones is filled by cartilages, fibrous bands, fatty tissues and synovial fluid. The joint is air-tight, and, as was first demonstrated by the Weber brothers, the atmospheric pressure keeps all parts in close apposition. This force is sufficiently great in the case of the hip-joint to support the whole weight of the leg even after all the surrounding soft parts have been cut through. The proof that the air-pressure gives this support is found in the fact that the head of the femur maintains its place in the acetabulum after all the soft parts which surround the joint have been divided, but falls out of its socket if a hole be bored in the acetabulum and air be permitted to enter the cavity of the joint. Though the air-pressure keeps the bones in constant contact it offers no resistance to the movements peculiar to the joints.

The movements of the bones is effected chiefly by muscular contractions, but the direction and extent of the movements is for the most part determined by the form of the joint-surfaces and the limitations to movement which result from the method of attachment of the ligaments. In the case of *sliding joints*, in which the articular surfaces are nearly flat, a sliding movement may occur in various directions, but the extent of the movement is slight, being limited by the capsule and the ligaments. *Hinge joints* have but a single axis of rotation, because the convex and somewhat cylindrical surface of one bone fits quite closely the concave surface of the other, and because of tense lateral ligaments which permit of movements only in a single plane. The joint between the humerus and the ulnar at the elbow is an example. The knee-joint[2] is a less simple form of hinge joint. The presence of the semilunar cartilages and

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[1] *Quain's Anatomy*, vol. ii. pt. 1.

[2] W. Braunne and Fischer have studied with mathematical accuracy the construction and movements of many of the joints of the human body. Their articles are published in the *Abhandlungen der math.-phys. Classe der königl. Sächsischer Gesellschaft der Wissenschaften*, Bd. xvii., and others.

the shape of the joint-surfaces cause flexion to be produced by the combined action of sliding, rolling, and rotation movements. In complete extension the lateral ligaments and the posterior and anterior crucial ligaments are put on the stretch, and there is a locking of the joint, no rotation being possible; in complete flexion, on the other hand, the posterior crucial ligament is tight, but the others are sufficiently loose to allow of a considerable amount of pronation and supination. In the *saddle-joint* there is a double axis of rotation—*e. g.* the articulation of the trapezius with the first metacarpal bone permits of rotation about an axis extending from before backward, and another, at nearly right angles to this, extending from side to side.

The *ball-and-socket joint*, of which the shoulder- and hip-joints are examples, permits of the greatest variety of movements, any diameter of the head of the bone serving as an axis of rotation.

Method of Action of Muscles upon the Bones.—The bones can be looked upon as levers actuated by the forces which are applied at the points of attachment of the muscles. All three forms of levers are represented in the body; indeed, they may be illustrated in the same joint, as the elbow.

An example of *a lever of the first class*, in which the fulcrum is between the power and the resistance, is to be found in the extension of the forearm in such an act as driving a nail: the inertia of the hammer, hand, and forearm offers the resistance, the triceps muscle acting upon the olecranon gives the power, and the trochlea, upon which the rotation occurs, is the fulcrum. The balancing of the head upon the atlas is another example: the front part of the head and face is the resistance, the occipito-atlantoid joint the fulcrum, and the muscles of the neck the power.

In the case of *a lever of the second order*, the resistance is between the fulcrum and the power; for example, when the weight of the body is being raised from the floor by the hands: the fulcrum is where the hand rests on the floor, the weight is applied at the elbow-joint, and the power is the pull of the triceps on the olecranon. The raising of the body on the toes is another example: the fulcrum is at the place where the toes are in contact with the floor, the resistance is the weight of the body transmitted through the tibia to the astragalus, and the power is applied at the point of attachment of the tendo Achillis to the os calcis.

The raising of a weight in the hand by flexion of the forearm through contraction of the biceps gives an example of *a lever of the third order*, in which the power is applied between the fulcrum and the weight. This form of lever, because of the great length of the resistance arm, as compared with the power arm, is favorable to extensive and rapid movements, and is the most usual form of lever in the body.

The power is applied to best advantage when it is exerted at right angles to the direction of a lever, as in the case of the muscles of mastication and of the calf of the leg. If the traction be exerted obliquely, the effect is the less the more acute the angle between the tendon of the muscle and the bone; for example, when the arm is extended the flexor muscles work to great disad-

vantage, for a large part of the force is expended in pulling the ulnar and radius against the humerus, and is lost for movement, but as the elbow is flexed the force is directed more and more nearly at right angles to the bones of the forearm, and there is a gain in leverage, which is of course again decreased as flexion is completed. This gain in leverage which accompanies the shortening of the muscles is the more important, since the power of the muscle is greatest when the muscle has its normal length, and continually lessens as the muscle shortens in contraction. There are a number of special arrangements which help to increase the leverage of the muscles by lessening the obliquity of attachment—viz. the enlarged heads of the bones, and in some cases special processes projecting from the bones, the introduction of sesamoid bones into the tendons, and the presence of pulley-like mechanisms.

The contraction of a muscle causes the points to which it is attached to approach one another, and the direction of the movement is often determined by the direction in which the force of the contracting muscle is applied to the bones. In the case of certain joints, however, the form of the joint-surfaces and the method of attachment of the ligaments limits the direction of movement to special lines; and when this is not the case the movement is usually the resultant of the action of many muscles rather than the effect of the contraction of any one muscle. This question has been made the subject of careful study by Fick.[1]

In the case of many muscles, both of the bones to which they are attached are movable, and the result of contraction depends largely on which of the extremities of the muscles becomes fixed by the contraction of other muscles. Though most muscles have direct influence over only one joint, there are certain muscles which include two joints between their points of attachment, and produce correspondingly complex effects. The accurate adjustment and smooth graduation of most co-ordinated muscular movements is due to the fact that not only the muscles directly engaged in the act, but the antagonists of these muscles take part in the movement. It would appear from the observations of certain writers[2] that antagonistic muscles may be not only excited to contraction, but inhibited to relaxation, and that the tension of the muscles is thereby accurately adjusted to the requirements of the movement to be performed. The importance of the elastic tension and reflex tonic contractions of muscles to ensure quick action, to protect from sudden strains, and to restore the parts to the normal position of rest has been referred to elsewhere.

The shape of the muscle has an important relation to the work which it has to perform. A muscle consists of a vast number of fibres, each of which can be regarded as a chain of contractile mechanisms. The longer the fibre, the greater the number of these mechanisms in series and the greater the total shortening effected by their combined action; consequently, a muscle with long fibres, such as the sartorius, is adapted to the production of extensive movements. In order that a muscle shall be capable of making powerful

[1] *Hermann's Handbuch der Physiologie*, 1871, Bd. i. pt. 2, p. 241.
[2] Sherrington: *Proceedings of the Royal Society*, Feb., 1893, vol. liii.

movements it is necessary that many fibres shall be placed side by side, as in the case of the gluteus : " Many hands, light work."

Standing.—In spite of the ease with which the many joints of the body move, the erect position is maintained with comparatively little muscular exertion. It is an act of balancing in which the centre of gravity of the body is kept directly over the base of support. In the natural erect position of the body the centre of gravity of the head is slightly in front of the occipito-atlantoid articulation, so that there is a tendency for the head to rock forward, as is seen from the nodding of the head of one falling asleep. The centre of gravity of the head and trunk together is such that the line of gravity falls slightly behind a line drawn between the centres of the hip-joints, which would incline the body to fall backward. The line of gravity of the head, trunk, and thighs falls slightly behind the axis of the knee-joints, and the line of gravity of the whole body slightly in front of a line connecting the two ankle-joints, so that the weight of the body would tend to flex the knee- and ankle-joints.

We cannot here consider in detail the mechanical conditions which limit the movements possible to the different joints in the erect position of the body. Although these conditions help to support the body in the upright position, they are not alone sufficient to the maintenance of this posture, as is shown by the fact that the cadaver cannot be balanced upon its feet. That standing requires the action of the muscles is further proved by the fatigue which is experienced when one is forced to stand for a considerable time. The body may be supported in the standing position in various attitudes. Thus, the soldier standing at " attention " places the heels together, turns the toes out, makes the legs straight and parallel, so as to extend the knees to their utmost, tilts back the pelvis, straightens the spine, and looks directly forward. In this position many of the muscles are relieved from action, for the complete extension of the knee, by bringing the line of gravity slightly in front of the axis of rotation and tending to produce further extension, puts the ligaments on the stretch and so locks the joint. Similarly, in the case of the hip-joint the tilting backward of the pelvis causes the line of gravity to fall slightly behind the joint and puts the strong ilio-femoral ligament on the stretch. The ankle-joint cannot be locked, and the tendency of the body to fall forward is resisted by the strong muscles of the calf of the leg. The erect position of the spine and the balancing of the head have likewise to be maintained by the action of muscles. Although this position gives great stability, it cannot be long maintained with comfort. It is less fatiguing to allow the joints to be a little more flexed, and to keep the balance by the action of the muscles, the position being frequently changed so as to bring fresh muscles into action. Perhaps the most restful standing position is found in letting the weight of the body be supported on one leg, the pelvis being tilted so as to bring the weight of the body over the femur, and the other being used as a prop to preserve the balance. Absolute stability in standing is impossible for any length of time ; the body is continually swaying, and a pencil resting on a writing

surface placed upon the head is found to write a very complicated curve. There is a normal sway for every individual, and this may become markedly exaggerated under pathological conditions. The maintenance of equilibrium requires that afferent impulses shall continually pass to the co-ordinating centres which control the muscles involved in this act, and if any of these normal impulses fail the sway of the body is increased; for example, it is more difficult to stand steadily when the eyes are closed than when they are open; the absence of the normal sensory impulses from the skin of the feet, the muscles, joints, etc., also makes standing more difficult and tends to increase the sway. The effect of the normal sway of the body is to shift the pressure and strain from point to point and to relieve the different muscles from continuous action.

Locomotion.[1]—The movements of animals were first studied by careful observation, accompanied by more or less accurate direct measurements, and by these simple methods the Weber brothers[2] arrived at quite accurate conclusions as to the nature of the processes, walking, running, jumping, etc. These results were greatly extended by Marey,[3] who employed elaborate recording methods, and exact pictures of all stages of these processes were later obtained through the remarkable revelations of instantaneous photography.[4]

Walking.—During the act of walking, at the same time that the body is propelled forward it is continually supported by the feet, one or the other of which is always touching the ground. Preparatory to beginning the movement the weight of the body is thrown upon one leg, while the other leg is placed somewhat behind it, the knee and ankle being slightly flexed. At the start the body is given a slight forward inclination, then the back leg is extended and impels the body forward. As the centre of gravity progresses so as to be no longer over the supporting leg, it would fall were it not that the back leg is at the same instant swung forward to sustain it. As the body moves forward and its weight is received by the leg which has just been advanced, the leg which has been its support is freed from the weight and becomes inclined behind it. This leg and foot are next extended, the body thereby receiving another forward impulse, and then the hip-, knee-, and ankle-joints flexing slightly, the leg swings forward past the supporting leg and again becomes the support of the body. The forward movement of the body is due in part to a slight inclination which tends to cause it to fall forward, and in part to a push given it by each leg in turn as it leaves the ground.

The amount of work performed by the legs in ordinary walking is comparatively slight, since the swing of the leg is, like that of a pendulum, largely

[1] Beaunis: *Physiologie humaine,* 1888, vol. ii. p. 269, gives many references to the literature of this subject.

[2] W. and E. Weber: *Mechanik der menschlichen Gehewerkzeuge,* 1836.

[3] *La Méthode graphique,* 1885.

[4] Marey: *Méthode graphique (supplement),* 1885; Muybridge: *The Horse in Motion, as Shown by Instantaneous Photography,* 1882.

a passive act. Speed in walking is attained by inclining the body somewhat more and by flexing the legs somewhat more, so that the hind limb in extending can push the body forward with greater force. The more rapid movement of the body is also accompanied by a more rapid forward swing of the leg, the muscles aiding the force of gravity. The transfer of the weight of the body from one leg to the other causes it to oscillate slightly from side to side, and the falling motion, interrupted by the support offered by the receiving limbs, causes a slight up-and-down movement. These oscillations are, however, very slight; the tendency for the centre of gravity to move from side to side as the legs alternately push the body forward is in part balanced by the swing of the opposite arm; and the vertical oscillation is largely obviated, because the supporting leg is extending—*i. e.* lengthening—as the body moves forward, and so sustains the pelvis until its weight is taken by the other leg.

In *running* the body is inclined more than in walking, and the legs are more flexed in order that the extension movement of the back leg, which drives the body forward, may be more effective. In running the body is propelled by a series of spring-like movements and there are times when both feet are off the ground, the back leg leaving the ground before the other touches it. The increase in speed is due in part to the greater forward inclination of the body, but more especially to the vigorous action of the muscles.

B. Voice and Speech.

1. Structure of the Larynx.

Voice-production.—The human voice is produced by vibration of the true vocal cords, normally brought about by an expiratory blast of air passing between them while they are approximated and held in a state of tension by muscular action. Mere vibration of the cords could produce but a feeble sound; the voice owes its intensity both to the energy of the expiratory blast (Helmholtz)[1] and to the reinforcement of the vibrations by the resonating cavities above and below the cords.

A true conception of the action of the larynx can only be gained by a preliminary study of the organ *in situ*, in its relations with the trachea, pharynx, tongue, extrinsic muscles, and hyoidean apparatus. Removed from its connections, the larynx, in vertical transverse section, is seen to be shaped somewhat like an hour-glass, the true vocal cords forming the line of constriction half way between the top of the epiglottis and the lower border of the cricoid cartilage (Fig. 295). In median vertical section the axis of the larynx above the vocal cords extends decidedly backward, and below the cords the axis is nearly perpendicular to the plane in which they lie. The epiglottis is an ovoid lamella of elastic cartilage, shaped like a shoe-horn, that leans backward over the laryngeal orifice so that the observer must look down obliquely in order to inspect the cavity of the larynx (Fig. 299). The mucous membrane is thickened into a slight prominence, known as the "cushion," at the base of

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[1] Quoted by Grützner: *Hermann's Handb. der Physiologie*, Bd. 11, Th. 2, S. 14, 1879.

the epiglottis.   The epiglottis, which is extremely movable in a median plane, may be tilted backward so as to close completely the entrance into the larynx.

Functions of the Epiglottis.—One function of the epiglottis seems obviously to serve as a cover for the superior entrance of the larynx, over which it is said to shut in the act of swallowing.   But it is found that deglutition occurs in a normal manner when the epiglottis is wanting or is too small to cover the aperture, the sphincter muscles surrounding the latter being capable of protecting the larynx against the entrance of foreign substances.   It is held by some that the epiglottis has an important influence in modifying the voice according as it more or less completely covers the exit to the column of vibrating air.   It is also held that the epiglottis acts as a sort of sounding-board, taking up and reinforcing the vibrations of the air-column impinging against it.[1]
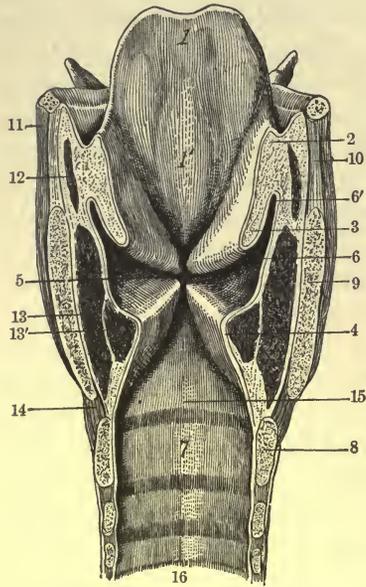
Fig. 295.—Vertical transverse section of the larynx (after Testut): 1, posterior face of epiglottis, with 1′, its cushion; 2, aryteno-epiglottic fold; 3, ventricular band, or false vocal cord; 4, true vocal cord; 5, central fossa of Merkel; 6, ventricle of larynx, with 6′, its ascending pouch; 7, anterior portion of cricoid; 8, section of cricoid; 9, thyroid, cut surface; 10, thyro-hyoid membrane; 11, thyro-hyoid muscle; 12, aryteno-epiglottic muscle; 13, ·thyro-arytenoid muscle, with 13′, its inner division, contained in the vocal cord; 14, crico-thyroid muscle; 15, subglottic portion of larynx; 16, cavity of the trachea.

Sweeping downward and backward from each edge of the epiglottis is a sheet of mucous membrane, the *ary-epiglottic fold*, which forms the lateral rim of the superior aperture of the larynx and which ends in, and covers posteriorly, the arytenoid cartilages.   The rounded prominence on the posterior corner of this fold is made by the cartilage of Santorini, and a second, less marked, swelling external to it, by the *cartilage of Wrisberg* (Fig. 302).   Looking down into the larynx, it is seen that its lateral walls approach each other by the development on each side of a permanent ridge of mucous membrane, known as the *ventricular band* or *false vocal cord* (Fig. 295).

Ventricular Bands and Ventricles of Morgagni.—*The ventricular bands or false vocal cords* arise from the thyroid cartilage near the median line, a short distance above the origin of the true cords.   They are inserted into the arytenoid cartilages somewhat below the apices of the latter.   Their free border is more or less ligamentous in structure.   They are brought into contact by the sphincter muscles of the larynx, and thus protect the glottis.   It has even been stated that, in paralysis of the true cords, they may be set in vibration and be the seat of voice-formation.   So-called "œdema of the glottis" is chiefly due to accumulation of fluid in the wide lymph-spaces found in the false cords.

[1] Mills: *Journ. of Physiology*, 1883, vol. iv. p. 135.

The ventricular bands are parallel with and just above the true vocal cords, from which they are separated by a narrow slit. They do not, however, reach so near the middle line as the true cords, which can be seen between and below the bands. The ventricular bands project more or less into the cavity of the larynx like overhanging lips, so that each band forms the inner wall of a space closed by the true vocal cords below, and communicating with the cavity of the larynx through the narrow slit above mentioned. The spaces thus bounded internally by the false cords are known as

The Ventricles of Morgagni (Fig. 295).—No complete explanation has been offered as to the purposes served by the ventricles of Morgagni and the false vocal cords. Numerous mucous and serous glands seated in the ventricular bands pour their secretions into the ventricles, whence the fluid may be transmitted by the overhanging lips of the ventricular bands to the true vocal cords; hence, an important function of the former structure, probably, is to supply to the vocal cords the moisture necessary to their normal action. The secretion contained within the ventricle is protected by the ventricular band from the desiccating influence of the passing air-currents. The existence of the ventricular spaces also permits free upward vibration of the true cords. The ventricles of Morgagni in some of the lower animals, as the higher apes, communicate with extensive cavities which serve an obvious purpose as resonating chambers for the voice, and perhaps the preservation of this function in the ventricles themselves is still of importance in the human being. It is not improbable that the ventricular bands find their most important function as sphincters of the larynx, the superior opening of which may be firmly occluded by their approximation. The well-known fact that during strong muscular effort the breath is held from escaping is, according to Brunton and Cash,[1] due to the meeting of the false cords in the middle line. The overhanging shape of the cords allows them to be readily separated by an inspiratory blast, but causes them to be more firmly approximated by an expiratory effort. This mechanism recalls the mode of action of the semilunar valves of the heart.

The true vocal cords arise from the angle formed by the sides of the thyroid cartilage where they meet in front, a little below its middle point, and, passing backward, are inserted into the vocal processes of the arytenoid cartilages. The aperture between the vocal cords and between the vocal processes of the arytenoids is known as the *glottis* or *rima glottidis* (Figs. 301, 302). Since, as will be seen later, the vocal cords may be brought together while the vocal processes of the arytenoids are widely separated at their bases, the space between the cords themselves is sometimes called the *rima vocalis* and that between the vocal processes the *rima respiratoria*.

In the adult male the vocal cords measure about 15 millimeters in length and the vocal processes measure 8 millimeters in addition. In the female the cords are from 10 to 11 millimeters in length. The free edges of the cord are thin and straight and are directed upward; their median surfaces are flattened. Each cord is composed of a dense bundle of fibres of yellow elastic tissue,

[1] Brunton and Cash: *Journ. Anat. and Phys.*, 1883, vol. xvii.

which fibres, though having a general longitudinal course, are interwoven, and send off shoots laterally into the subjacent tissue. The compact ligament, known commonly as the " vocal cord," forms only the free edge of a reflexion from the side wall of the larynx. This reflexion is wedge-shaped in a vertical, transverse section and contains much elastic tissue and the internal and part of the external thyro-arytenoid muscle (Fig. 295). This whole structure properly forms the vocal cord, and by contraction of its contained muscle its thickness and vibrating qualities may be greatly modified.

Like the trachea, the larynx, with the exception of the vocal cords, is lined
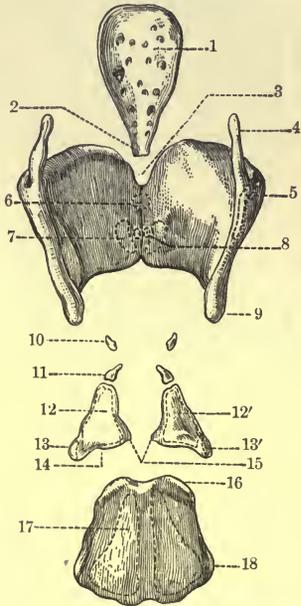
FIG. 296.—Cartilages of the larynx, separated (Stoerk): 1, epiglottis; 2, petiolus; 3, median notch of thyroid; 4, superior cornu of thyroid; 5, attachment of stylo-pharyngeus muscle; 6, origin of thyro-epiglottic ligament; 7, origin of the thyro-arytenoid muscle; 8, origin of true vocal cord ; 9, inferior cornu of thyroid; 10, cartilage of Wrisberg; 11, cartilage of Santorini; 12, 12′, arytenoid cartilages, showing attachments of the transverse arytenoid muscle; 13, 13′, processus musculares, showing attachments of the posterior and lateral crico-arytenoid muscles; 14, base of the arytenoid cartilage; 15, vocal processes of the arytenoids; 16, articular surface for the base of the arytenoid cartilage; 17, posterior view of cricoid cartilage, with outline of attachment of the posterior crico-arytenoid muscle; 18, articular surface for inferior cornu of thyroid cartilage.
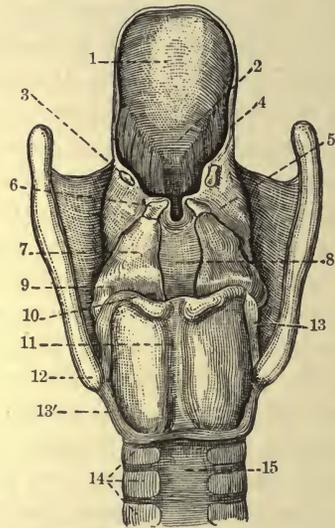
FIG. 297.—Cartilages and ligaments of the larynx; posterior view (after Stoerk): 1, epiglottis ; 2, cushion of the epiglottis; 3, cartilage of Wrisberg; 4, ary-epiglottic ligament; 5, 8, mucous membrane ; 6, cartilage of Santorini; 7, arytenoid cartilage; 9, its processus muscularis; 10, crico-arytenoid ligament; 11, cricoid cartilage; 12, inferior cornu of thyroid cartilage; 13, posterior superior cerato-cricoid ligament; 13′, posterior inferior cerato-cricoid ligament; 14, cartilages of the trachea; 15, membranous portion of trachea.

by columnar, ciliated epithelium, the direction of whose movement is upward toward the pharynx. The vocal cords are covered by thin, flat, stratified epithelium. The inner surface of the epiglottis, the walls of the ventricles, and the ventricular bands contain much adenoid tissue, the spaces of which are apt to become distended with fluid, giving rise to œdema of those parts. The whole mucous membrane of the larynx, except over the vocal cords, is richly supplied with glands both mucous and serous in character.

Cartilages of the Larynx.—The mechanism of the larynx is supported by a skeleton composed of several pieces of cartilage. The lowermost of these cartilages is the *cricoid* cartilage, so called from its resemblance to a signet ring (Fig. 296). The cricoid cartilage is situated above the topmost ring of the trachea to which it is attached by a membrane. The vertical measurement of the cricoid cartilage is about one inch on its posterior, and one-quarter inch on its anterior surface. Superior to, and partly overlapping the cricoid, is the *thyroid* cartilage, which forms an incomplete ring, being deficient posteriorly (Fig. 296). The free corners of the thyroid behind are prolonged upward or downward into projections known as the *cornua.* The upper pair are attached to the extremities of the greater cornua of the hyoid bone, while by the inner surface of the ends of the lower cornua the thyroid is articulated with the cricoid cartilage and rotates upon it around an axis drawn through the points of articulation. The lower anterior border of the thyroid cartilage is evenly concave, but its upper border has a deep narrow notch in the middle line. The upper half of the thyroid in front projects sharply forward in an elevation known as *Adam's apple* (*pomum Adami*), which is much more marked in adult males than in females. The elliptical space between the cricoid and thyroid cartilages in front is covered by a membrane. Adam's apple, the anterior part of the cricoid ring, and the space between the two, can easily be felt in the living subject; they rise perceptibly toward the head with each swallowing movement.

The arytenoid cartilages are two in number and are similar in shape (Figs. 296, 297). Each cartilage, which has somewhat the form of a triangular pyramid, is seated on, and articulates with, the highest point on the posterior part of the cricoid cartilage some distance from the middle line. Of the free faces of the pyramid, one looks backward, one toward the middle line, and the third outward and forward. Each face is more or less concave. The apex of each arytenoid cartilage is capped by a small body called the *cartilage of San-torini* or, from its bent shape, *corniculum laryngis* (Figs. 296, 297). Outside and in front of the latter is the minute *cuneiform cartilage* or *cartilage of Wrisberg*, enclosed in the ary-epiglottic fold. The lateral posterior corner of the arytenoid cartilage forms a blunt projection which serves for the attachment of muscles, the *processus muscularis.* The anterior, lower, and median part of each cartilage is of especial interest, since it serves for the posterior attachment of the vocal cord; it is known as the *processus vocalis.*

The thyroid and cricoid cartilages and the body of the arytenoids are of hyaline cartilage, and tend to become ossified in middle life. The other cartilages and the vocal processes of the arytenoids are composed of the elastic variety.

The Muscles of the Larynx may be divided into two classes—the *extrinsic* and the *intrinsic;* the former find their origin outside the larynx, and the latter both arise and are inserted within it.

Extrinsic Muscles.—To this group belong the *sterno-hyoid*, the *sterno-thyroid*, and the *omo-hyoid* muscles, which depress the larynx or hyoid bone; the *thyro-hyoid* muscle, which depresses the hyoid bone or elevates the thyroid

cartilage. To the elevators of the larynx belong the *genio-hyoid*, the *mylo-hyoid*, the *digastric*, the *stylo-hyoid*, and the *hyo-glossus*. The muscles of the palate and the constrictors of the pharynx enter into coördinated action with the above. When food is passing through the pharyx in the act of swallowing, the hyoid bone is drawn upward and forward, raising the larynx with it; the tongue is thrown backward so that the epiglottis covers the entrance into the larynx, and the constrictors of the larynx contract, completely closing the entrance into that organ.

The *intrinsic muscles* of the larynx are the *crico-thyroids*, the *lateral crico-arytenoids*, the *posterior crico-arytenoids*, the *arytenoid*, the *aryteno-epiglot-tideans*, and the *thyro-arytenoids;* all being in pairs except the arytenoid, which crosses the middle line. The *crico-thyroid* muscle arises from the front and side of the cricoid cartilage and, passing upward and backward, is inserted into the lower edge of the thyroid cartilage (Fig. 298). The action of the crico-thyroid muscle is to diminish the distance between the thyroid and cricoid car-tilages in front, either by depressing the front of the thyroid or by elevating that of the cricoid cartilage, or both. In the first case the distance between the anterior attachment of the vocal cords and the vocal processes of the arytenoid cartilages is increased by movement of the thyroid, and in the second case the same effect is produced by backward rotation of the edge of the cricoid upon which the arytenoid cartilages are seated (Fig. 297). The muscle, therefore, is a tensor of the vocal cords. It is, probably, the mechanism we ordinarily use in raising the pitch of the voice when the vocal machinery has been " set " by the other muscles (see below). If the fingers be placed on the cricoid ring and on the *pomum Adami* while the ascending scale is sung in the middle chest register, both descent of the front of the thyroid and ascent of the cricoid can be made out. The *lateral crico-arytenoid* muscle arises from the upper, lateral border of the cricoid cartilage, and passes upward and backward to be inserted into the outer edge of the arytenoid car-tilage, on and in front of the lateral prominence (Fig. 299). Its main action is to wheel the vocal process of the arytenoid toward the middle

FIG. 298.—Lateral view of the cartilages of larynx with the crico-thyroid muscle (*Quain's Anatomy,* after Willis): 1, crico-thyroid mus-cle; 2, crico-thyroid membrane; 3, cricoid cartilage; 4, thyroid carti-lage; 5, upper rings of the trachea.

line and thus approximate the vocal cords. The *posterior crico-arytenoid* is a large muscle, which rises from the median posterior surface of the cricoid car-tilage and passes upward and outward to be inserted into the outer surface of the arytenoid cartilage, behind and above the insertion of the lateral crico-arytenoid (Fig. 300). Its action is to turn the vocal processes outward and thus abduct the vocal cords. The posterior crico-arytenoid occupies an important position in the group of respiratory muscles; during vigorous inspiration it is brought into action

and widens the glottis. Paralysis of this muscle is a most serious condition, since it is followed by approximation of, and inability to separate, the vocal cords. The *arytenoid*, or *transverse* or *posterior arytenoid* muscle, the single unpaired
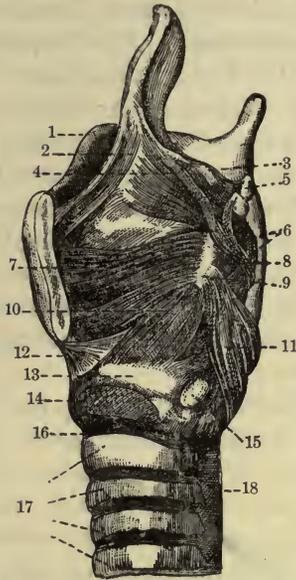
FIG. 299.—Larynx and its lateral muscles after removal of the left plate of the thyroid cartilage (Stoerk): 1, thyroid cartilage; 2, thyro-epiglottic muscle; 3, cartilage of Wrisberg; 4, ary-epiglottic muscle; 5, cartilage of Santorini; 6, oblique arytenoid muscles; 7, thyro-arytenoid muscle; 8, transverse arytenoid muscle; 9, processus muscularis of arytenoid cartilage; 10, lateral crico-arytenoid muscle; 11, posterior crico-arytenoid muscle; 12, crico-thyroid membrane; 13, cricoid cartilage; 14, attachment of crico-thyroid muscle; 15, articular surface for the inferior cornu of the thyroid cartilage; 16, crico-tracheal ligament; 17, cartilages of trachea; 18, membranous part of trachea.
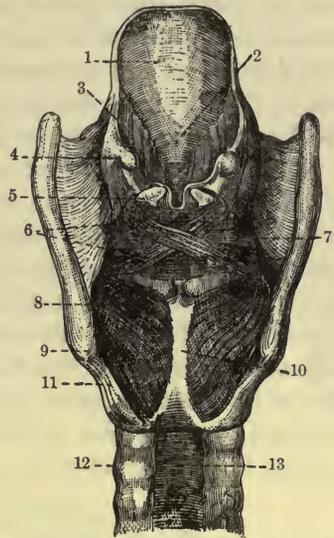
FIG. 300.—Larynx with its muscles, posterior view (Stoerk): 1, epiglottis; 2, cushion; 3, ary-epiglottic ligament; 4, cartilage of Wrisberg; 5, cartilage of Santorini; 6, oblique arytenoid muscles; 7, transverse arytenoid muscle; 8, posterior crico-arytenoid muscle; 9, inferior cornu of thyroid cartilage; 10, cricoid cartilage; 11, posterior inferior cerato-cricoid ligament; 12, cartilaginous portion; 13, membranous portion of trachea.

muscle of the larynx, is a considerable band passing across the middle line from the posterior surface of one arytenoid cartilage to that of the other (Fig. 300). Its action is to draw the arytenoid cartilages together in the middle line and approximate the vocal processes; its action is essential in closing the glottis. In the resting larynx the arytenoid cartilages are kept apart by the elastic tension of the parts. The *aryteno-epiglottidean*, sometimes called the *oblique arytenoid*, muscles consist of two bundles of fibres seated upon the surface of the arytenoid muscle (Fig. 300). Each muscle arises from the outer posterior angle of the arytenoid cartilage, and, passing upward and inward, crosses in the middle line partly to be inserted into the outer and upper part of the opposite cartilage, partly to penetrate the ary-epiglottic fold as far as the epiglottis, and the remainder to join some fibres of the thyro-arytenoid muscle. The action of the aryteno-epiglottidean muscles is to close the glottis. The *thyro-arytenoid* is a muscle of complex mechanism, usually described as formed of two parts, an external and an internal. The external thyro-arytenoid arises from the lower

part of the angle of the thyroid cartilage; its fibres pass, for the most part, backward and somewhat upward and outward to be inserted into the outer edge of the arytenoid cartilage and its lateral *processus muscularis* (Figs. 295, 301). Some of its bundles of fibres, however, have different directions, and a portion of them pass upward into the ventricular bands. The internal *thyro-arytenoid*, wedge-shaped in transverse section, lies between the muscular division just described and the vocal ligament, by which its thin median edge is covered. The internal thyro-arytenoid arises from the anterior angle of the thyroid cartilage and is inserted into the *processus vocalis* and the outer face of the arytenoid cartilage. Certain fibre-bundles of this, as of the external division of the muscle, pass in various directions, some of them being inserted into the free border of the vocal cord. The action of the muscle is, on the whole, to draw the arytenoids forward and thus relax the vocal cords; but, by its contraction, the cords may also be approximated and their thickness, and probably their elasticity, extensively modified.

Specific Actions of the Laryngeal Muscles.—To sum up the various effects of the muscular action on the larynx: A *sphincter action* of the larynx is brought about by the combined contraction of all the muscles with the exception of the crico-thyroids and the posterior crico-arytenoids; *the vocal cords are adducted and the glottis narrowed* by the transverse and oblique arytenoids, the external thyro-arytenoids, and the lateral crico-arytenoids; *the vocal cords are abducted and the glottis widened* chiefly or wholly by the posterior crico-arytenoids; *the vocal cords are made tense* by contraction of the crico-thyroids; *the vocal cords are slackened* by the combined action of the sphincter group and especially by the external thyro-arytenoids.
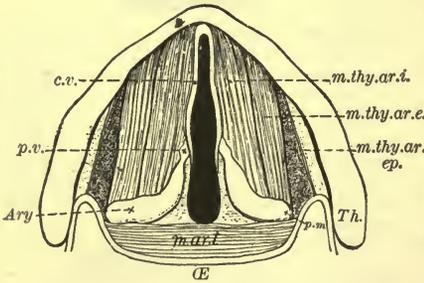
FIG. 301.—Diagram to illustrate the thyro-arytenoid muscles; the figure represents a transverse section of the larynx through the bases of the arytenoid cartilages (redrawn from Foster): *Ary,* arytenoid cartilage; *p.m,* processus muscularis; *p.v,* processus vocalis; *Th,* thyroid cartilage; *c.v,* vocal cords; *Œ* is placed in the œsophagus; *m.thy.ar.i,* internal thyro-arytenoid muscle; *m.thy.ar.e,* external thyro-arytenoid muscle; *m.thy.ar.ep,* part of the thyro-ary-epiglottic muscle, cut more or less transversely; *m.ar.t,* transverse arytenoid muscle.

It will easily be seen that in the larynx, as in the skeleton at large, the efficiency of any single muscle involves the action of accessory muscles; thus, contraction of the crico-thyroid could have little effect in tightening the vocal cords were not the arytenoid cartilages fixed by contraction of the posterior crico-arytenoid and arytenoid muscles.

Nerve-supply of the Larynx.—The larynx receives its nerve-supply from the superior and the inferior or recurrent laryngeal nerves. The extremely sensitive surface of the mucous membrane of the organ above the vocal cords is supplied by sensory filaments of the superior laryngeal nerve. The superior laryngeal also supplies motor fibres to the crico-thyroid muscle, whose action as a tightener of the vocal cords is peculiar. All the other muscles of the

larynx receive their motor impulses from the inferior laryngeal nerve. Much of the nervous mechanism of the larynx is still in dispute.

Laryngoscopic Appearance of the Larynx.—Much may be learned by inspection of the larynx during life by means of the laryngoscopic mirror. It is not difficult for an observer to examine his own larynx by placing himself before a second mirror in which may be seen the image reflected from the laryngoscope. To inspect the larynx the tongue must be held well out so as to pull forward the epiglottis, then the structures below appear in the laryngoscopic mirror in reversed position. Beneath the middle of the epiglottis the cushion may be seen as a slight swelling, and continuing downward and backward from the edges of the cartilage, may be seen the ary-epiglottic folds, each marked at its extremity by two rounded nodules, the cartilages of Wrisberg and Santorini (Fig. 302). In quiet breathing the glottis is nearly stationary and opened to the extent of from 3 to 5 millimeters. The vocal cords bounding it look white and glistening in contrast with the red color of the general mucous membrane. The cartilages of Santorini are several millimeters apart, and a sheet of mucous membrane reaches from one to the other. The ventricular
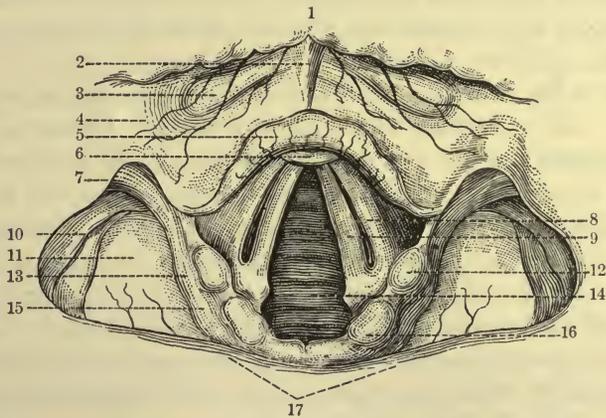
FIG. 302.—The laryngoscopic image in easy breathing (Stoerk): 1, base of the tongue; 2, median glosso-epiglottic ligament; 3, vallecula; 4, lateral glosso-epiglottic ligament; 5, epiglottis; 6, cushion of epiglottis; 7, cornu major of hyoid bone; 8, ventricular band, or false vocal cord; 9, true vocal cord; opening of the ventricle of Morgagni seen between 8 and 9; 10, folds of mucous membrane; 11, sinus pyriformis; 12, cartilage of Wrisberg; 13, aryteno-epiglottic fold; 14, rima glottidis; 15, arytenoid cartilage; 16, cartilage of Santorini; 17, posterior wall of pharynx.

bands are seen as red shelves reaching to the outer margin of the shining cords and separated from the latter by a dark line which is the entrance into the ventricles of Morgagni.

When a deep inspiration is taken the glottis is widely opened, even to the extent of half an inch; an angle is formed between the vocal process of the arytenoid and the vocal cord, the space between the cartilages of Santorini is widened, and the rings of the trachea, and even its bifurcation may be seen below. With the succeeding expiration the glottis again becomes narrow. When the voice is sounded the picture at once changes. The space between the cartilages of Santorini is obliterated, the vocal processes and cords are

brought together, and the whole rim of the glottis or the vocal cords alone, according to the pitch of the note, may be seen to vibrate.

2. THE VOICE.

The vocal machinery consists of—(1) the motive power or breath; (2) the larynx, which forms the tone; (3) the chest, the pharynx, the mouth, and the nose, which color the tone; and (4) the organs of articulation.[1]

The production of voice is undoubtedly accomplished by the vibration of the vocal cords which have previously been approximated in the middle line and made tense through action of the nerve-muscular apparatus already described. A blast of air from below pressing against the cords so adjusted, causes them to separate and fall into vibration. We have to distinguish in voice the three features of *loudness*, *pitch*, and *quality*.

The *loudness* of the tone depends on two factors: (1) the strength of the tone-producing blast as determining not only the amplitude of vibration of the vocal cords, but also the energy with which the air is expelled; (2) the resonance of the two chambers between which the vocal cords are suspended, the chest below and the cavities of the head above, whose walls and contained air, by their sympathetic vibration, powerfully reinforce the oscillations imparted to them.

The *pitch* of the voice is determined by the thickness, tension, and length of the vocal cords, conditions which regulate the pitch of the note obtained from any vibrating string. The thickness and the elastic quality of the cords are probably largely under the control of the thyro-arytenoid muscle. The principal tensor of the cords is the crico-thyroid muscle. Other muscles, as described above, may so fix the arytenoid cartilages that their vocal processes may be prevented from taking part in the vibration of the cords throughout the whole and also, possibly, throughout part only of their length. This dampening of the vocal processes of the arytenoids may be accomplished either by pressure applied to them throughout their whole length, in which case the posterior part of the glottis is closed, or they may be pressed together at the tips alone, leaving the respiratory glottis open as a triangular aperture.

Quality.—Variation in the *quality* of the voice depends on the fact that vibrations of the vocal cords are composite in character, giving rise to notes made up of a fundamental tone combined with upper partial tones (see p. 827). By reason of the varied adjustments that may be imparted to it, the larynx is capable of producing many more qualities of tone than is any artificial instrument.[2] Change in the size and shape of the resonance-chamber above and below the vocal cords produces a corresponding change in their fundamental notes and, therefore, in the partial tones of the voice which they reinforce by sympathetic vibration (see p. 829). According to Helmholtz,[3] the difference in quality between the various vowel sounds of the human voice depends on

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[1] C. H. Davis: *The Voice*, 1879.
[2] Helmholtz: *Sensations of Tone*, trans. by Ellis, 1885, p. 98.
[3] *Op. cit.*, p. 104.

the number and relative prominence of the various overtones determined by altering the shape and size of the nasal and buccal resonance-chambers.

By a simple experiment the production of voice by the vocal cords can easily be illustrated. Take a glass tube, about ½ inch in diameter and of convenient length, and press one end firmly against the palmar surfaces of the proximal phalanges of two fingers at their line of division when they are brought together. By blowing smartly into the other end of the tube, a musical note will be produced by the vibration of the folds of the skin between which the air is forced. By relaxing the pressure with which the fingers are held together, the length of the vibrating segment of skin is increased and its tension diminished; its note is accordingly lowered. The reverse conditions are produced when the fingers are held together tightly and the tube applied firmly; the pitch of the note is then raised. In these ways the pitch of the note may be varied through two octaves, which is the range of a good singing voice. Various upper partials of the note so produced may be made prominent by sympathetic resonance, if the vibrating air-stream is sent across the opening of a wide-mouthed bottle, of about a pint capacity. The air within the bottle is thrown into sympathetic vibration when its fundamental tone is contained in the note emitted through the fingers; when the volume of the air is diminished by slowly pouring water into the bottle, the fundamental tone of the resonator is changed, and it responds to one after another of the partials contained in the musical note.

The marvellous adjustment of muscular action by which, at will, notes may be struck of definite pitch and quality, is evidence of an elaborate nervous machinery for the larynx, not only on the efferent side but, possibly through a muscular sense, on the afferent side as well. The various phenomena of aphasia, and the anatomical importance of the cerebral areas devoted to the elaboration of speech, point in the same direction. The relations between the centres for speech and hearing are most intimate. The ear plays a constant part, as a critical medium, in the tuition of the vocal organs in either speech or song. So-called " dumbness" is the result, usually, not of defects in the vocal organs, but of lack of hearing and, hence, of inability to control by the ear the pitch or quality of the vocal notes.

The voice and the larynx of the child fall naturally in a group with those of the female as contrasted with the adult male. At the age of puberty a boy's larynx becomes congested and undergoes rapid development. The voice changes rapidly from the juvenile to the adult quality. During this change, the voice frequently "breaks" or rapidly returns from the newly-acquired chest register to the head or falsetto notes of childhood (see p. 873). In boys who are castrated a good while before the age of puberty is reached, the larynx does not undergo its characteristic development, and the voice remains of a peculiar quality, much valued in some countries in the rendition of vocal music. The practice of castration for æsthetic purposes has, accordingly, in certain districts, long been in vogue. In the female the changes in the larynx and in the voice at puberty are much less marked than in the male.

Arrangements for Changing the Pitch of the Voice.—As has frequently been mentioned, the vocal cords are stretched, and the pitch of their note is elevated, by contraction of the crico-thyroid muscle. But the change that is thus produced in the tension of the vocal cords is by no means capable of accounting for the full range of pitch which falls within the compass of the voice. When the arytenoid and the crico-arytenoid muscles sufficiently contract, the vocal processes are brought tightly together and their vibration is prevented. Voice-production must then be limited to the vocal cords themselves, and the stretching action of the crico-thyroids may begin anew and reach its maximum with the glottis so set that only its ligamentous borders can vibrate. It can also be seen that the vocal cords themselves may be shortened functionally, or even be broken up into segments, or the main body of the cord be changed in thickness, by contraction of the complex thyro-arytenoid muscles; each such condition would be accompanied by a change in the rate of vibration. We are probably justified in assuming that, when the musical scale is sung, the lowest notes are produced by vibration of the glottic borders throughout their full length, and the elevation of pitch is affected by the gradually-increased tension of the vocal ligaments through the action of the crico-thyroid muscle. This contraction having reached its maximum, the muscle probably relaxes, only to contract again after the vibrating segments of the glottis are shortened by a partial or complete clamping together of the vocal processes in the manner described above. There are thus two or three, or more, adjustments which may be imparted to the vibrating mechanism of the larynx, each of which is distinguished by giving rise to a note of different pitch that may further be altered by action of the crico-thyroid muscle. It might be anticipated that the voice whose pitch was gradually elevated in the manner described would suffer some alteration in quality at those points in the scale where there is a change in the *set* of the larynx producing a shortening of the vibrating segment. Such, indeed, is the fact.

Registers.—Long before the invention of the laryngoscope, and before anything definite was known of the method of voice-production, it was recognized that in ascending the musical scale there occur certain breaks, as it were, where the voice changes in quality as well as in pitch. It is an object in musical education to render these breaks as little prominent as possible. The kinds of voice included between these breaks were distinguished as the vocal "registers." There is no general agreement among musicians as to how many registers are compassed by the voice, and the nomenclatures used to distinguish them differ in the most confusing fashion. According to some authors, the range of the voice is included within two registers only; more commonly three distinct registers are described, to which, in certain cases, a fourth is said to be probably added. The most common designation of the lowest register is the " chest voice," though it has also been called " thick "[1] as distinguished from the " thin " register; another term applied to it is the " long-reed " register as con-

[1] Browne and Behnke: *Voice, Song, and Speech*, 1890, p. 135.

trasted with the "short-reed" register.[1] The middle register of all voices is by some authors (Garcia,[2] Mme. Seiler[3]) denominated the "falsetto," while other writers use this term to distinguish certain higher notes of the male voice of a peculiar quality not in ordinary use. The third and highest series of vocal sounds is usually known as the "head" register.

The lowest or chest register is that used in ordinary life. It is so called from the strong vibrations of the chest-wall which may be felt while the voice is sounded. In passing to the higher register the chest vibration is found to diminish and that of the head bones to increase; in the one case the cavity of the head acts strongly as a resonance chamber, and in the other that of the thorax. According to Madame Seiler, in the lowest register both the vocal ligaments and the vocal processes of the arytenoids vibrate. In the middle register the vocal processes are clamped together and the vibration of the ligaments seems confined chiefly to their sharp edges; while in the highest register the ligaments themselves appear to be damped throughout the greater part of their length, the vibrations being confined to the edges of an oval slit at their
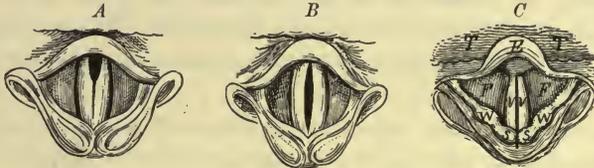
Fig. 303.—The voicing (female) larynx (after Browne and Behnke). *A,* Small or highest register. *B,* Upper thin or middle register. *C,* Lower thin or middle register: *T,T,* tongue; *F,F,* false vocal cords; *S,S,* cartilages of Santorini; *W,W,* cartilages of Wrisberg; *V,V,* vocal cords.

anterior ends (Fig. 303). Within any definite register the quality of individual voices is determined by the size and elasticity of the parts of the larynx, and probably also by peculiarities of the resonating chambers; voices are accordingly classified as base, tenor, alto, and soprano.

A Whistling Register.—A friend and former pupil of the author's has the remarkable power of emitting from the larynx notes which are indistinguishable in quality from an ordinary whistle. He writes, "The whistle cannot be made to 'slide' into vocal tones of any sort, nor can any other tones be produced simultaneously with it. Its range is about one and a half octaves, or half an octave less than my singing voice.

"The lips have nothing to do with the sound except as their position changes the resonance-quality of the tone by 'reinforcement' or otherwise, for I can whistle almost as readily with the teeth closed and the lips wide parted as with the jaws and lips firmly closed as in the ordinary position. Any other movement of the air-column destroys the sound at once." Some years ago the author made a laryngoscopic examination of this larynx while it was in the act of whistling. No notes were written at the time, but the picture remembered is that of vocal cords closely approximated, except for an oval slit between their anterior and middle portions, as in singing head tones, the cords vibrating chiefly along their free edges.

Speech.—*Language* consists, in general, of a combination of short musical sounds, *vowels* or *sonants*, which are produced purely by vibration of the vocal

[1] Mackenzie: *Hygiene of the Vocal Organs,* 1891, p. 55.
[2] Garcia: *Lond., Edin., and Dub. Mag.,* vol. x. 1855, p. 218. (Quoted by Seiler.)
[3] Seiler: *op. cit.*

cords, together with superadded noises or modes of obstruction, *con-sonants*, produced by action of the mouth-parts. The vowel sounds usually carry the accent of syllables, and the consonants, for the most part, are sounded only with, or represent peculiar modes of obstructing the former. No classification of vocal signs can be made in which exceptions do not form important *addenda* to general rules.

Articulation is the modification of sound in speech, usually effected by action of the lips, the tongue, the palate, or the jaws, and the place of articulation depends, in any definite case, on the mode in which a sound is formed. Its use as an expression of thought is the chief physiological distinction between man and the lower animals. Distinctness of articulation, so essential to clearness of language, not to mention its æsthetic value, depends on the accuracy of the muscular adjustments used in forming sounds, especially consonantal sounds.

The *speaking* is distinguished from the *singing voice* partly by the fact that most sounds in the first case are articulate or formed in the mouth, while in the latter their quality is only there modified. In singing the tone is sustained at the same pitch for a considerable interval, while in speaking the voice is continually sliding up and down on the vowel sounds. In speaking the consonantal noises and obstructions are more prominent because of their more abrupt formation.[1,2]

Vowel sounds owe their origin to vibration of the vocal cords, and their quality to the selective resonance of the cavities above the cords. In sounding the series of vowels, *a, e, i, o, u* (pronounced ah, a, e, o, oo), it is found that the
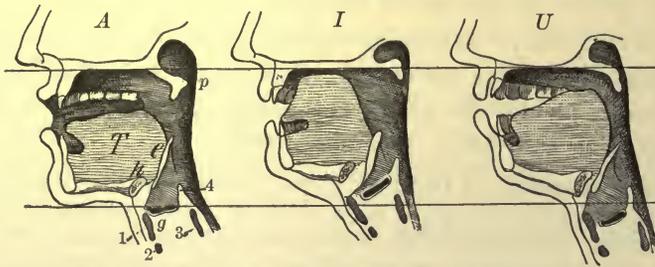
FIG. 304.—Section of the parts concerned in phonation, and the changes in their relations in sounding the vowels *A* (ᵃʰ), *I* (ᵉᵉ), *U* (ᵒᵒ) (after Landois and Stirling): *T*, tongue; *p*, soft palate; *e*, epiglottis; *g*, glottis; *h*, hyoid bone; 1, thyroid; 2, 3, cricoid; 4, arytenoid cartilage.

form and size of the mouth-cavity, the position of the tongue, the position of the soft palate separating or allowing communication between the nasal and pharyngeal cavities, undergo a progressive change (Fig. 304). Helmholtz has shown that the vowel sounds owe their differences of quality to the varied resonance of the mouth-cavity, dependent on its shape, through which now one, now another, of the overtones in the note produced by vibration of the vocal cords is reinforced.[3] This result is dependent on the fact that when the mouth is set in position for the formation of the various vowel sounds the pitch of its

[1] Browne and Behnke: *op. cit.*, p. 28.
[2] Monroe: *Manual of Physical and Vocal Training*, 1869, p. 51.
[3] Helmholtz: *loc. cit.*

fundamental note, or the rate of vibration to which it sympathetically responds, varies accordingly.[1] That the resonance of the mouth cavity changes with its shape is illustrated in the various pitch of the notes produced by flipping the edge of an incisor tooth, the cheek, or Adam's apple with the finger-nail, while the mouth assumes the positions for production of the different vowels.

Vowels whose normal pitch is low, as *o*, *u*, cannot be sounded easily in the higher part of the musical scale; conversely, high-pitched vowels, as *e* in *feet*, lose their character in the lower part of the scale. Language is, therefore, much less distinct in song than in speech.[2]

Since the mouth cavity is set to a definite pitch for each vowel sound, it follows that when the same vowel is voiced in different parts of the musical scale, those tones which are strengthened by resonance remain the same, but their distance from the fundamental will be different. That is, the resonated partial depends not only on its relation to the fundamental, but also on its vibration rate.[3] This feature of vocal resonance distinguishes the human larynx from most musical instruments. That the ground is not covered by these facts was shown by Auerbach,[4] who demonstrated that the strength of upper partials in vowel sounds depends also on the strength of their production by the vocal cords and, therefore, upon their relation to the fundamental tone. That is to say, the quality of a vowel is dependent not only on the *absolute* vibration numbers of its upper partials, according to which they are or are not reinforced by the position of the mouth, but also on the *relative* position of these upper partials as compared with the fundamental tone.

The peculiar æsthetic value of the human voice is dependent on the fact that, on account of its varied powers of adjustment, the larynx is capable of producing many more kinds of tone-quality than any artificial instrument. Helmholtz[5] found no less than sixteen overtones to accompany the fundamental.

The posture of the mouth-parts differs markedly when set for the various principal vowel sounds; but as we know that each vowel sound has several modifications or gradations so that a tone may pass by an easy glide from one to another, so the form of the mouth passes by insensible steps from one vowel position to another. It will be seen later that several articulate sounds play the part now of vowels, now of consonants, according to their position in the syllable or mode of formation. There has also been shown reason for believing that the form of the chest cavity and the tension of its walls are factors in determining the pitch of its fundamental tone; so that through the varied sympathetic resonance of the thorax the reinforcement of laryngeal tones may here be altered somewhat, as in the mouth itself.[6, 7]

Whispering is a mode of speech in which noise largely replaces pendular musical vibrations. The glottis remains more or less widely open and the vocal cords are not tense; the vibrations are produced both in the larynx and in the buccal-pharyngeal chambers. Vowel sounds may be produced in whis-

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[1] Helmholtz: *op. cit.*, p. 108.   [2] *Op. cit.*, p. 114.   [3] *Op. cit.*, p. 118.
[4] Quoted by Grützner: *op cit.*, p. 179.   [5] *Op. cit.*, p. 103.   [6] *Op. cit.*, p. 93.
[7] Sewall and Pollard : *Journal of Physiology*, vol. xi., 1890, p. 159.

pering as well as in true voice because, from the multitude of irregular vibrations, those waves are reinforced which make up the vowel sounds determined by the set of the mouth. Gentle whispering requires much less effort than does speaking, and inspiratory whispering is less easily distinguished from expiratory than is the strained voice of inspiration from the natural sound of expiration. Consonants, as already indicated, may sometimes play the part of vowels, but pure consonants do not appear in syllables except in combinations with vowels, which combinations always carry the syllable accent.

Consonants.—The distinction between consonants and vowels lies in the fact that the tones of the latter are produced by vibration of the vocal cords, the parts above which act only as resonance-boxes and modify the sound, and never offer marked obstruction to the exit of air; whereas in the formation of consonants there is some adjustment in the mouth-passage either in the nature of a local narrowing, by which a peculiar noise is added to the vocal sound, or in the nature of a sudden closing or opening of the air-channel by which a characteristic noise is likewise added to the vocal sound. In other words, the parts above the larynx *make* the sounds of consonants but only *modify* those of vowels.[1] No sharp line of separation can be drawn between vowels and consonants, since certain characters, according to their associations, now fall into one, now into another class. In the classification of consonantal sounds much confusion exists, dependent chiefly on the fact that several letter characters change their modes of formation and expression with their place in the syllable. The same facts, also, are expressed by different authors by different nomenclatures, and sounds occur in one language that are not found in another. Adopting the general classification of Grützner,[2] we may divide consonants into the following three groups:

1. *Semi-vowels* or *liquids*, which can be used either as vowels or consonants; this group includes the sounds *m, n, ng, l,* and *r*. In expressing the function of a consonant, the letter is not to be sounded as if it stood alone, but its character given as actually expressed in a syllable; thus the sound of *p* is not *pee*, but is the abbreviated labial expression, as in *pack* or *piece* when all the letters are eliminated after the first. Of the liquids the *n, m,* and *ng* (sometimes called "resonants") have the nature of vowels when final (as in *him, hen, being*), and are then produced by vibration of the vocal cords, the lips having previously been closed for the *m*, and the tongue applied to the roof of the mouth to cut off the exit of air for *n* and *ng;* the expelled air escapes altogether through the nose, which acts as a resonance-chamber. Used as consonants, as in *make* and *no, m* and *n* are seen to have the characters of the second group,—Explosives. *L* is pronounced somewhat like *n*, but air is allowed to escape through the mouth on each side of the tongue; it may be produced either with voice or without voice (in whispers). It may have vowel characters as in *play*. *R* is characterized as a *vibrative* and may have several seats of articulation, as by the thrill of the tip of the tongue against the hard palate, or that of the hind part of the tongue against the soft palate, or even

[1] Grützner: *op. cit.*, p. 196.　　　　　　　　　　[2] *Op. cit.*, p. 197.

by the coarse vibration of the vocal cords themselves. In the first two cases it may be sounded either with or without voice. Its vowel nature is shown in such words as *pray.*

2. *Explosives,* which are produced either when an obstruction is suddenly offered to or removed from the exit of air from the mouth; at the same time a characteristic noise is produced. They may be subdivided according to the place of articulation into *labials* (*p, v*); *linguo-palatals* (*t, d*); *gutturals* (*k, g*). The similarity in the method of formation of *p* and *b, t* and *d, k* and *g,* is striking. They are frequently characterized as being formed *with* or *without* voice; that is, *b, d,* and *g* require voice for their distinct recognition, and when whispered they are easily mistaken for *p, t, k,* which latter do not require voice (vibration of the vocal cords) for their recognition. A consonant, then, is said to be formed *with voice* when it can be rendered distinctly only by an accompanying vibration of the vocal cords, *without voice* when articulated clearly without laryngeal aid. The former are sometimes called *sonants,* the latter *surds.* This classification only approximates the truth, for the suddenness and energy with which the obstruction to the breath is removed determines our recognition of the consonant irrespective of voice.[1]

Table of Consonantal Elements.[2]

PLACE OF ARTICULATION.	ORAL.				NASAL.
	Momentary.		Continuous.		Continuous.
	Surds (without voice).	Sonants (with voice).	Surds (without voice).	Sonants (with voice).	Sonants (with voice).
Lips	p	b	. . . . . .	w	m
Lips and teeth	. . . . . .	. . . . . .	f	v	
Tongue and teeth . . .	. . . . . .	. . . . .	th(in)	th(y)	
Tongue and hard palate (forward)	t	d	s	z, r	n
Tongue and hard palate (back)	ch	j	sh	zh, r	
Tongue, hard palate, and soft palate	. . . . . .	. . . . . .	. . . . . .	y, l	
Tongue and soft palate .	k	g	. . . . . .	. . . . .	ng
Various places	h				

3. *Friction* sounds or *frictionals,* often called *aspirates,* are all noises produced by the expired blast passing through a constriction in its passage, at which point a vibration is set up. No obstruction being offered to the sound, they are known as *continuous* as distinguished from the *momentary* sounds of group 2. They may be divided into *labio-dental frictionals, f* (without voice); *v, w* (with voice); the *lingual frictionals s, th* (as in *them*); *sh, ch* soft (without voice); *z, j* (with voice). The sound of *h* may be regarded as due to the vibration of the separated vocal cords. It is peculiar, however, in appearing to be formed in any part of the vocal chamber; when it is formed the mouth parts take on no peculiar position, but assume that of the vowel following the *h,* as *hark, hear,* etc.

[1] Grützner, *op. cit.,* pp. 211, 213.
[1] *Webster's International Dictionary,* 1891, p. lxvi.

XIII. REPRODUCTION.

THE principles and problems of Physiology that have been already presented in this volume, comprising nutrition and the functions of the muscular and the nervous systems, have reference to the individual man or woman. Through the normal activity of those functions and their appropriate coordination the individual lives his daily life or performs his daily tasks as an independent organism. But man is something more than an independent organism; he is an integral part of a race, and as such he has the instincts of racial continuance. The continuance of the race is assured only by the production of new individuals, and the strength of the human reproductive instinct is indicated in some measure by the large proportion of energy that is expended by woman in the bearing of children and by both sexes in the nurture and education of the young. The function of reproduction is not limited to the daily life and well-being of independent organisms. It has a deeper significance than that. Its essence lies in the fact that it has reference to the species or race. Many of its problems are, therefore, broad ones; they include not only the immediate details of individual reproduction, but larger ones relative to the nature and significance of reproduction and of sex, and to heredity. In the following discussion some of these broader applications of the facts presented will be indicated.

A. REPRODUCTION IN GENERAL.

In all forms of organic reproduction the essential act is the separation from the body of an individual, called the parent, of a portion of its own material living substance, which under suitable conditions is able to grow into an independent adult organism.

Among living beings two methods of reproduction are recognized, the asexual and the sexual methods. Both are widespread among animals and plants, but the asexual method is the more primitive of the two and is relatively more frequent in low organisms. The sexual method, the only one present in the production of new individuals among the higher animals, has evidently been acquired gradually, and has probably been developed from the asexual method.

Asexual Reproduction.—Asexual reproduction, or *agamogenesis*, is the chief method of reproduction among unicellular plants and animals, and throughout the plants and in the lower multicellular animals it is important. Among various species it takes various forms, known as fission or division, gemmation or budding, endogenous cell-formation or spore-formation or multi-

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ple fission ; but all the varieties are modifications of the simplest form, fission or division. In fission, found only in unicellular organisms and typified in *Amœba*, the protoplasm of the single cell, together with the nucleus, becomes divided into two approximately equal portions which separate from one another. In the process no material is lost, and two independent nucleated organisms result, each approximately half the size of the original. The parent has become bodily transformed into the two offspring, which have only to increase in size by the usual processes of assimilation in order themselves to become parents. In higher organisms, even where sexual processes alone prevail in the production of new individuals, the asexual method has persisted in the multiplication of the individual cells that constitute the body ; embryonic growth is an asexual reproductive process, a continued fission, differing from the amœboid type in the facts that the resulting cells do not separate from one another to form independent organisms, but remain closely associated, undergo morphological differentiation and physiological specialization, and together constitute the individual. Likewise in the adult the production of blood-corpuscles and of epidermis, the regrowth of lost tissues, and the healing of wounds are examples of asexual cell-reproduction. From the standpoint of multicellular growth Spencer and Haeckel have happily termed the process of asexual reproduction in unicellular organisms " discontinuous growth."

Sexual Reproduction.—Sexual reproduction, or *gamogenesis*, occurs in unicellular organisms, where it is known as conjugation, and is the prevailing form of reproduction in most of the multicellular forms. In most of the invertebrate and vertebrate animals it is the sole form of reproduction of individuals. In its simple form of conjugation, typified in the minute monad, *Heteromita*, it consists of a complete fusion of the bodies of two similar individuals, protoplasm and nuclei, followed by a division of the mass into numerous spore-like particles, each of which grows into an adult *Heteromita*. In the higher infusorian, *Paramœcium*, the fusion of the two similar individuals is a partial and temporary one, during which a partial exchange of nuclear material takes place ; this is followed by separation, after which each individual proceeds to live its ordinary life and occasionally to multiply by simple fission.

In the highly specialized sexual reproduction of higher animals, including man, the individuals of the species are of two kinds or sexes, the male and the female, with profound morphological and physiological differences between them ; in each the protoplasm of the body consists of two kinds of cells, somatic cells and germ-cells, the former subserving the nutritive, muscular, and nervous functions of daily life, the latter subserving reproduction. The germ-cells of the male, called *spermatozoa*, are relatively small and active, those of the female, called *ova*, are relatively large and passive ; the reproductive process consists of a fusion of a male and a female germ-cell, the essential part being a fusion of their nuclei ; and this is followed by continued asexual cell-division and growth into a new individual. Among both plants and animals it is not

difficult to find a series of forms showing progressively greater and greater deviations from the typical asexual toward the typical sexual method of reproduction, and the existence of such a series is indicative of the derivation of the latter from the former type.

Origin of Sex, and Theory of Reproduction.—It is obvious that the production of new individuals is necessary to the continued existence of any species. It would be interesting to know the origin and significance of the two existing methods of reproduction. Apropos of the asexual process, Leuckart, and especially Herbert Spencer, have pointed out that during the growth of a cell the mass increases as the cube, but the surface only as the square, of the diameter—*i. e.* the quantity of protoplasm increases much more rapidly than the absorptive surface. It follows from this that during the growth of a unicellular organism a size will ultimately be reached beyond which the cell will not be able to absorb sufficient food for the maintenance of the proto-plasm. In order that growth may continue beyond this point, a division of the cell, which ensures a relative increase of surface over mass, is absolutely necessary. Fission is, therefore, a necessary corollary of growth, and, although we are ignorant of the details of its mechanism, it is conceivable that the method of asexual reproduction arose through causes connected with growth.

The explanation of sexual reproduction is much more difficult, for here, in addition to the budding off of the germ-cells from the parental bodies, which has probably the same fundamental cause as fission in unicellular forms, we must account for the differentiation into sexes, the existence of special sexual cells, and the fusion of the male and the female germinal substance; in short, we must account for the conception of sexuality itself and all that it implies.

Regarding the origin of sexuality itself, as to the question whether sexuality is an original and fundamental attribute of protoplasm or has been acquired, we may say at once that at present we know really nothing. Yet, whatever view is held as to the origin of sexuality, it seems entirely probable that the method of reproduction known as sexual is a derivative of the method known as asexual—the latter is primitive, the former has arisen from it. From the wide distribution and prominence of the former among vital phenomena we must believe, with biologists generally, that sexual differentiation and sexual processes have arisen from natural causes, and for the reason that sexual repro-duction is of advantage to living beings and to species. In what way it is of advantage, however, is disputed. Three views, all of which have evidence in their favor and which are not mutually exclusive, are at present engaging the attention of scientific men. The first to be mentioned is the theory advocated by Hensen, Edouard van Beneden, and Bütschli, according to whom the fusion of the cells in sexual reproduction exists for the purpose of rejuvenating the living substance. The power possessed by cells of dividing asexually is limited; in time the protoplasm grows old and degenerates; its vital powers are weakened, and without help the extinction of the race must follow. But the mingling of another strain with such senescent protoplasm gives it renewed youth and vigor, restores the power of fission, and grants a new lease of life to

the species. From his observations upon the Infusoria, Maupas[1] has brought forward valuable evidence which has been quoted in favor of this view. *Stylonychia* normally produces by fission 130 to 180 generations or individuals, *Onychodromus* 140 to 230, and *Leucophrys patula* 300 to 450, after which conjugation is necessary to continued division. If conjugation be prevented, the individuals become small, their physiological powers become weakened, their nuclei atrophy, and the chromatin disappears; all of which changes are evidence of the oncoming of senile degeneration, and this ultimately results in death. Analogous to this is doubtless the fact, pointed out by Hertwig,[2] that in sexual animals an unfertilized ovum within the oviduct soon becomes over-mature and enfeebled, and subsequent fertilization, even though possible, is abnormal. Even if the idea of "rejuvenescence" be regarded as fanciful and as a comparison rather than an explanation, it seems to be a principle of nature that occasional fusion of one line of descent with another is necessary to continued reproduction and continued life.

A second theory, defended by Hatschek and Hertwig, argues that sexual reproduction prevents variation, and thus preserves the uniformity of the race. The mingling of two different individuals possessing different qualities must give rise to an individual intermediate between the parents, but differing from them. Such differences between parents and offspring are numerous, but in a single generation are minute, and they are easily obliterated by a subsequent union, which latter in turn gives rise to other minute differences. Hence sexual reproduction, although constantly producing variations, as constantly eradicates them, and, by striving always toward the mean between two extremes, tends toward homogeneity of the species. The essential truth of such a view seems obvious.

A third theory, advocated by Weismann and Brooks, is quite the opposite of the last, and maintains that the meaning of sexual reproduction lies in the production of variations. "The process furnishes an inexhaustible supply of fresh combinations of individual variations." These minute variations, seized upon by natural selection, are augmented and made serviceable, and a variety, better able to cope with the conditions of existence, results. The transformation, not the homogeneity, of the species is thereby assured. The two latter views are not necessarily mutually exclusive. Both claim that fertilization brings into evidence variations. It is quite conceivable that subsequent fertilizations may obliterate some and augment others, the result of union being the algebraic sum of the characteristics contributed by the two sexes.

Primary and Secondary Characters.—In the human species, as in all the higher sexual animals, the characters of sex, anatomical, physiological, and psychological, are divisible into two classes, called primary and secondary. Primary sexual characters are those that pertain to the sexual organs themselves and to their functions. They are naturally the most pronounced of all

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[1] E. Maupas: *Archives de Zoologie expérimentale et générale*, 2e série, vii., 1889.

[2] O. und R. Hertwig: *Experimentelle Studien am thierischen Ei vor, während und nach der Befruchtung*, i., 1890.

sexual attributes. Secondary sexual characters comprise those attributes that are not directly connected with the sexual organs, but that, nevertheless, constitute marked differences between the sexes; such are the greater size and strength of man's body as compared with woman's, the superior grace and delicacy of woman's movements, the deeper, rougher voice of man, and the higher, softer voice of woman. In reality, all secondary sexual characters are accessory to the primary ones, and the greater portion of the present article will be devoted to a discussion of the latter. The primary sexual characters of the male centre in the production of spermatozoa and the process of impregnation, those of the female in the production of ova and the care of the developing embryo.

Sexual Organs.—Sexual organs are classified into essential and accessory organs. The essential organs are the two *testes* of the male and the two *ovaries* of the female. The accessory organs of the male comprise the *vasa deferentia*, the *seminal vesicles*, the *urethra*, the *penis*, the *prostate gland*, *Cowper's glands*, and the *scrotum* and its attached parts. The accessory organs of the female comprise the *oviducts* or *Fallopian tubes*, the *uterus*, the *vagina*, the various external parts included in the *vulva*, and the *mammary glands*. During the greater part of life the sexual organs perform but a portion of their duties; only at intervals, and in some individuals never, do they complete the cycle of their functions by engaging in the reproductive process itself. In the following account we shall discuss first the habitual physiology of the organs of the male and of the female, and later their special activities in the reproductive process.

B. The Male Reproductive Organs.

The male reproductive organs, already mentioned, have as their specific functions the production of the essential male germ-cells, the spermatozoa, the production of a fluid medium in which the spermatozoa can live and undergo transportation, the temporary storing of this seminal fluid, and its ultimate transference to the outside world or to the reproductive passages of the female.

The Spermatozoon.—Spermatozoa were first discovered by Hamm, a student at Leyden, in 1677. Hamm's teacher, Leeuwenhoek, first studied them carefully. They were long believed to be parasites, even until near the middle of the present century, when their origin and fertilizing function were established. Spermatozoa are cells modified for locomotion and entrance into the ovum. Human spermatozoa are slender, delicate cells, averaging 0.055 millimeter ($\frac{1}{450}$ of an inch) in thickness, and consisting of a head, a middlepiece, and a tail (Fig. 305). The *head* (*h*) is flattened, egg-shaped, with a thin anterior edge and often slightly depressed sides. It terminates anteriorly in a slender projecting and sharply pointed thread or spear. Its chief component appears to be chromatic substance, and it is to be regarded probably as a nucleus covered by an excessively thin layer of cytoplasm. von Bardeleben[1]

[1] K. v. Bardeleben: *Verhandlungen der Anatomischen Gesellschaft; Anatomischer Anzeiger*, vii., 1892.

claims the number of chromosomes in the chromatic substance after matura-
tion to be eight.

The *middle-piece* (*m*) is a short, cytoplasmic rod, probably containing a cen-
trosome. The *tail* (*t*) is a delicate filiform, apparently cytoplasmic structure,
and analogous to a single cilium of a ciliated cell. The tail is tipped by an
excessively fine, short filament, the *end-piece* (*e*). The most
abundant of the solid chemical constituents of the spermato-
zoon is nuclein, probably in the form of nucleic acid, which
is found in the head. Other constituents are proteids, prota-
mine, lecithin, cholesterin, and fat.

The structure and power of movement of the spermatozoon
plainly show it to be adapted to activity. It is not burdened
by the presence of food-substance within its protoplasm. It
is the active element in fertilization; it seeks the ovum, and
it is modified from the form of the typical cell for the special
purpose of fertilization. The nucleus is the fertilizing agent.
The head is plainly fitted for facilitating entrance into the
ovum. The tail is a locomotor organ capable of spontaneous
movements, and, after expulsion of the semen, it propels the
cell, head forward, through the fluid in which it lies. The
movement is a complex one, and is effected by the lashing
of the tail from side to side, accompanied by a rotary move-
ment about the longitudinal axis. The rate of movement has
been variously estimated at from 1.2 to 3.6 millimeters in the
minute. Toward heat, cold, and chemical agents spermatozoa
behave like ciliated cells.

FIG. 305.—Human
spermatozoa (after
Retzius): *A*, sperm-
atozoon seen *en face*;
h, head; *m*, middle-
piece; *t*, tail; *e*, end-
piece; *B*, *C*, seen
from the side.

Ripe spermatozoa appear to be capable of living for months
within the male genital passages, where they are probably
quiescent. Outside of the body they have been kept alive and in motion for
forty-eight hours. It is not certain how long they may remain alive within
the genital passages of the human female. They have been found in the *os
uteri* and capable of movement more than eight days after their discharge. It
seems not improbable that within the female organs their environment is favor-
able to a somewhat prolonged existence. In this connection it is of interest to
know that spermatozoa capable of fertilizing have been known to live within
the *receptaculum seminis* of a queen bee for three years.

Spermatozoa are produced in large numbers. Upon the basis of observa-
tions in several individuals, Lode[1] computes the average production per week
as 226,257,000, and in the period of thirty years from twenty-five to fifty-five
years of age the total production as 339,385,500,000. This excessive produc-
tion is an adaptation by nature that serves as a compensation for the small
size of the cells and the small chance of every cell finding an ovum. With-
out large numbers fertilization would not be ensured and the continuance of
the species would be endangered.

[1] A. Lode: *Pflüger's Archiv für die gesammte Physiologie*, l., 1891.

Maturation of the Spermatozoon.—Considerable theoretical interest attaches to the question as to the real morphological value of the spermatozoon. It is undoubtedly a cell, and has arisen by division from one of the testicular cells, called the primary spermatocyte or sometimes the mother-cell of the spermatozoon. But is it the morphological equivalent of one of the mother-cells? In most animals, and probably also in man, each primary spermatocyte gives rise to four spermatids, which grow directly into four spermatozoa. The process of derivation of the spermatozoa may be called, by analogy with the process in the ripening of the ovum, maturation. The details and essence of the process have been much discussed. Van Beneden found in an interesting worm, *Ascaris*, that the number of chromosomes in the nucleus of a single spermatozoon is only half that in the original testicular cell; that is, the process of maturation of the spermatozoon consists in a reduction of the chromosomes by one half. This discovery has since been extended to many other forms, including mammals and man,[1] and it has been shown further that the mature spermatozoon contains only one-half the number of chromosomes characteristic of the tissue-cells of the species in question. In the light of the subsequent process of fertilization these facts are interesting. Hertwig and Weismann, who regard the chromatic substance of the nucleus as the bearer of the hereditary qualities, interpret this halving of the chromatin as a provision for the reduction of the hereditary mass, which later will be restored to its full amount by union with the egg. As we shall see, the maturation of the ovum follows a somewhat similar course, and, since the process has been more fully studied there, we shall reserve further discussion until that subject is reached (p. 889).

Semen.—Semen consists of spermatozoa, together with fluid and dissolved solids, coming partly from the testes themselves, but chiefly secreted by the accessory sexual glands—namely, the glands within the *vasa deferentia*, the seminal vesicles, the prostate gland, and Cowper's glands. It is a whitish, viscid, alkaline fluid, with a slight characteristic odor. The amount passed out at any one time has been estimated at between 0.5 and 6 cubic centimeters. Its chemical composition has not been examined exhaustively. Besides water, it contains approximately 18 per cent. of solid substances, which comprise nuclein, protamine, proteids, xanthin, lecithin, cholesterin, and other extractives, fat, and sodium and potassium chlorides, sulphates, and phosphates. Under proper treatment colorless crystals, called Charcot's crystals, may be obtained from semen. They appear to be a phosphate of a nitrogenous base, which has been called *spermine*. Interest in the semen centres in its histological rather than its chemical features. The fluid portion serves as a vehicle for the transportation of and possibly also for the nutrition of the ripe spermatozoa. Colorless particles, called seminal granules, exist in semen. They are possibly parts of nuclei of disintegrated cells. Comparatively little is known of the composition or the specific function of the individual secretions contributed by the various organs. The disintegration of the nutritive cells of the testis probably furnishes some of the

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[1] v. Bardeleben : *loc cit.*

nutritive substance of the fluid. Prostatic secretion is viscid and opalescent, and contains 1.5 per cent. of solids, comprising mainly proteids and salts. It contributes the substance of Charcot's crystals to the semen, and their partial decomposition is said to be responsible for the characteristic odor of the seminal fluid. The secretion from the seminal vesicles is fairly abundant, is albuminous, and in some animals at least seems to contain fibrinogen. This enables the fluid to clot after its reception in the female passages, and thus to prevent loss of spermatozoa. Cowper's glands secrete a mucous fluid. By careful experiments upon white rats Steinach[1] has shown that removal of the seminal vesicles and the prostate gland, while not diminishing the sexual passion and the ability to perform the sexual act, including the actual discharge of spermatozoa, prevents entirely the fertilization of the ova; removal of the seminal vesicles alone markedly weakens the fertilizing power of the semen. The secretions of these accessory glands are essential to the mobility of the spermatozoa, and they may have other important functions.

The Testis.—The testes (Fig. 306, t) are compound tubular glands with a unique structure. Formed early in embryonic life as solid structures, with the seminiferous tubules ($t.s$) represented by solid cords of cells, they remain in the embryonic condition until the time of puberty. Some of the cells, the mother-cells of the spermatozoa, then begin actively to divide, and the result of division with differentiation is the mature spermatozoa. These latter accumulate at the centre of the tubules, the walls being formed largely of the dividing cells or immature spermatozoa. Other cells do not produce spermatozoa, but seem to disintegrate and give rise to the nutritive fluid and nuclear particles that are found mixed with the sperm-cells. From the time of puberty on, usually throughout life, this cellular activity proceeds, the rate and regularity probably varying greatly with individuals and depending largely on the frequency of discharge of the semen. Spermatozoa

FIG. 306.—Diagram of the male reproductive organs: t, testis; $t.s$, seminiferous tubules; $t.r$, tubuli recti; $r.v$, rete vasculosum; $v.e$, vasa efferentia; e, canal of the epididymis; $v.a$, vas aberrans; $v.d$, $v.d$, vas deferens; $v.s$, seminal vesicle; $d.e$, ejaculatory duct; pr, prostate gland; b, urinary bladder; $C.g$, Cowper's gland; u, urethra; pn, penis.

may be wanting in old men, but they have been found in individuals at eighty or ninety years of age. The spermatozoa accumulate within the seminal

[1] E. Steinach: *Pflüger's Archiv für die gesammte Physiologie*, lvi., 1894.

tubules, and by the constant formation of others behind them are gradually pushed outward along the ducts.

The Ducts of the Testis.—The ducts of the testis (Fig. 306) comprise a succession of tubes of different morphological and physiological values. They are approximately twenty-five feet in length, and are named, in order, *tubuli recti, rete vasculosum, vasa efferentia, canal of the epididymis, vas deferens,* and *ejaculatory duct.* The *tubuli recti* (*t.r*) and *rete vasculosum* (*r.v*), being mere channels for the passage of spermatozoa, present no special physiological features. The *vasa efferentia* (*v.e*) and the *canal of the epididymis* (*e*) contain smooth muscular tissue in their walls, and, moreover, are lined by ciliated epithelium, the cilia causing a movement outward ; both of these features doubtless aid in the outward passage of the spermatozoa. The excretory duct of the testis, or *vas deferens* (*v.d*), with its offshoot, the seminal vesicle, is more important physiologically. It is nearly two feet in length, with a diameter throughout the greater part of its course of one-tenth of an inch. Near its termination, however, it is larger and sacculated, and resembles the seminal vesicle ; it is known here as the *ampulla of Henle.* Its epithelium is not ciliated, but its walls contain a very thick, plain muscular layer consisting of outer longitudinal and inner circular fibres. In the walls of the ampulla of Henle exist small tubular glands. The *vas deferens* is an important storehouse for the spermatozoa. The glands near its termination supply a part of the fluid of the semen. The muscles in its walls, by contracting, aid in the seminal discharges. The *seminal vesicle* (*v.s*) is a branched diverticulum from the vas deferens. In structure it is not radically unlike the ampulla of Henle, its walls containing muscular layers and glands. Its chief, if not its only, function is to contribute fluid to the semen. Of all the organs, the seminal vesicles contribute probably the greatest share of fluid. Microscopic examination does not confirm the old belief that the vesicles are storehouses for semen, and this idea is now largely laid aside. The *ejaculatory duct* (*d.e*) on each side is a short, thin-walled muscular tube, passing partly through the substance of the prostate gland and serving to convey the semen to the urethra.

The Urethra.—The *urethra* (Fig. 306, *u*), the common excretory duct for the urine and the semen, is commonly described as consisting of three parts, named, respectively, the prostatic, the membranous, and the spongy portions. The first is characterized by the presence of the prostate gland, the second by the absence of special features, and the third by the presence of Cowper's glands and the penis. Throughout its length the wall of the urethra contains plain muscular tissue arranged longitudinally within and circularly without ; and, except at the external opening, the small racemose mucous *glands of Littré.* Its wall is hence contractile and its lumen is kept moist. Beyond these its special physiological features are given it by the organs above mentioned.

The Prostate Gland.—The *prostate gland* (Fig. 306, *pr*) is a compound tubular gland whose alveoli are mingled with a large quantity of plain muscular tissue. It completely surrounds the urethra at the base of the bladder,

and opens into it by numerous small ducts situated about the openings of the *vasa deferentia*. Its function is to contribute prostatic fluid to the semen. The composition of this fluid has been already mentioned (p. 885); its specific use is not known.

Cowper's Glands.—*Cowper's glands* (Fig. 306, *C.g*), two in number, are tubulo-racemose glands, the ducts of which open into the spongy portion of the urethra by two orifices situated some two inches below the openings of the *vasa deferentia*. Their viscid secretion is thought to be one of the components of the seminal fluid, but its specific function is unknown. It has been suggested that Cowper's fluid cleanses the urethra of urine and of semen, instead of contributing actually to the seminal fluid.

The Penis.—The *penis* (Fig. 306, *pn*) has as its constant function merely the conveying of the urine to the outside world, and for this purpose it has no special features beyond those belonging to the urethra, which runs throughout its whole length. Specifically, however, it is the intromittent organ, and serves to convey the semen into the genital passages of the female. This function is based upon its power of erection, and this power is dependent upon the presence of the erectile tissue which constitutes the bulk of the organ. The erectile tissue is arranged in the form of three long cylindrical masses imperfectly separated from, but parallel to, one another and extending lengthwise. Of these, the two *corpora cavernosa* lie at the sides, and meet each other in the middle line along the upper side of the penis; the *corpus spongiosum* lies in the middle line below, and is pierced throughout its length by the urethra. At its proximal end each corpus is enlarged into a bulbous part, and is covered by a layer of muscular fibres constituting a distinct muscle—the bulbs of the *corpora cavernosa* by the *ischio-cavernosi* (*erectores penis*), that of the *corpus spongiosum* (called *bulbus urethræ*) by the *bulbo-cavernosus* (*accelerator urinæ*). At its distal end each *corpus cavernosum* terminates bluntly, while the *corpus spongiosum* projects farther and enlarges to form the extremity of the organ, the *glans penis*. Each corpus is spongy in consistence, being formed of a trabecular framework of white and elastic connective tissue and plain muscular fibres, with cavernous venous spaces, and is covered by a tough fibrous tunic. When the spaces are distended with blood the whole organ becomes hard, rigid, and erect in position. The mechanism of erection will be studied more in detail later (p. 901). The penis, especially toward its termination, is beset with end-bulbs, Pacinian bodies, and other nerve-terminations, that make it particularly sensitive to external stimulation.

C. The Female Reproductive Organs.

The female reproductive organs, already mentioned, have as their specific functions the production of the essential female germ-cells, the *ova*, their transference to the uterus, and, if unfertilized, to the outside world; if fertilized, the protection and nutrition of the developing embryo, its ultimate transference to the outside world, and the nutrition of the child during early infancy.

The Ovum.—The human ovum was discovered in 1827 by Von Baer, and it was he who first completely traced the connection between ova in the generative passages and ova in the Graafian follicles of the ovary. The conception of ova as the essential female element had, however, long been held, and Harvey's dictum of the seventeenth century, that everything living is derived from an egg (*omne vivum ex ovo*), is well known. The human ovum, as it comes from the ovary, is a spherical, protoplasmic cell (Fig. 307), averaging with the *zona radiata*, approximately 0.2 millimeter ($\frac{1}{127}$ inch) in diameter. As in other cells, the cell-body may be distinguished from the nucleus, the protoplasm of the former being called *cytoplasm*. In its finer structure the cytoplasm consists of an excessively delicate network of protoplasmic substance. As in other mammalian eggs, it probably contains, adjoining the nucleus, a minute, specially differentiated portion, consisting of a single or double *centrosome* surrounded by an *attraction sphere* (Fig. 308, *A*). For some distance inward from the border the cytoplasm is pure and transparent, and this portion is often called the protoplasmic zone (Fig. 307, *p*). Throughout the centre of the cell, however, it is obscured by the presence of an abundance of yolk-substance, or *deutoplasm*, from which the corresponding part of the ovum is sometimes called the deutoplasmic zone (*d*). Deutoplasm is non-living substance; it consists of granules of yolk imbedded in the meshes of the cytoplasmic network, and, like its analogue, the yolk of the hen's egg, it serves as food for the future cells of the embryo.
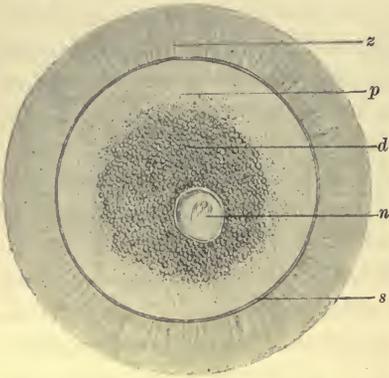
FIG. 307.—Human ovum (modified from Nagel): *n*, nucleus (germinal vesicle) containing the amœboid nucleolus (germinal spot); *d*, deutoplasmic zone; *p*, protoplasmic zone; *z*, zona radiata; *s*, perivitelline space.

A comparison of the respective amounts of food in the human and the fowl's egg, with the manner of embryonic development, is suggestive. The chick develops outside the body of the hen, and, therefore, requires a large supply of nutriment, which it finds in the yolk and the white of the egg. The child develops within the mother's body and receives its nourishment from the maternal blood; hence the supply of food within the egg is only enough to ensure the beginning of growth, special blood-vessels being formed to facilitate its continuance.

The *nucleus* (*n*), commonly called by its early name, the *germinal vesicle*, is spherical, and usually occupies a slightly eccentric position. Its protoplasm consists of a network composed of two kinds of material: the more delicate, slightly staining threads are the *achromatic substance*, the coarser, deeply staining portion, the *chromatic substance* or *chromatin*. The former is continuous with, and probably of exactly the same nature as, the cytoplasm.

The chromatin is peculiar to the nucleus, and at certain stages in the nuclear history is resolved into distinct granules or filaments, the *chromosomes* (Fig. 308, *A*), the number of which in the human ovum is unknown. There is much reason for believing that the chromatin is the bearer of whatever is inherited from the mother. The nucleus is limited by a nuclear membrane, and contains a strongly marked *nucleolus*, which has likewise retained its original name of *germinal spot*. There is probably no proper cell-wall, or *vitelline membrane*, such as is said to exist in many mammalian and other eggs. The ovum is, however, surrounded by a thick, tough, transparent membrane of ovarian origin, about 0.02 millimeter ($\frac{1}{1270}$ inch) in thickness, and called the *zona radiata* or *zona pellucida* (Fig. 307, *z*). It is pierced by a multitude of fine lines radiating from the surface of the zona to the ovum; these are thought to represent pores, to contain fine protoplasmic processes of the surrounding ovarian cells, and thus to serve as channels for the passage of nutriment to the egg. Between the *zona radiata* and the ovum a narrow space, the perivitelline space (*s*), exists. Attached to the outside of the *zona radiata* are usually patches of cells derived from the *discus proligerus* of the Graafian follicle of the ovary, which may form a complete covering and constitute the *corona radiata*. They disappear soon after the egg is discharged from the ovary.

Regarding the chemistry of the mammalian ovum little is known definitely, and of the human ovum nothing whatever except by inference from the eggs of lower animals. The protoplasmic basis undoubtedly resembles other undifferentiated protoplasm in its general composition, with an abundance of proteid among its solid constituents. Deutoplasm is a rich mixture of food-substance in concentrated form, and contains among its solids probably vitellin, nuclein, albumin, lecithin, fats, carbohydrates, and inorganic salts.

The form and the structure of the egg suggest the part that it plays in reproduction. It is not locomotor; in fertilization it is the passive element; it remains in its place and is sought by the spermatozoon. Its nucleus is the equivalent of that of the spermatozoon. Its form renders easy the entrance of the male element. Its bulk consists largely of food in a very concentrated form, and, as development proceeds, it supplies this food to the growing cells.

In lower forms of animal life, where eggs are fertilized outside the body of the parent in the water into which they are set free, they are usually produced in enormous numbers. Some fail of fertilization, while others are destroyed by enemies, and the large number is a compensatory adaptation by nature for their poor chance of survival. In mammals and man, however, ova have a much better opportunity of being fertilized and of developing into adults, and their number is correspondingly reduced. Their relative fewness, as compared with the spermatozoa, is in harmony with their larger size and the fact that, while awaiting fertilization, they are carefully protected within the body of the mother.

Maturation of the Ovum.—Attention has been called to the maturation of the spermatozoon. The ovum undergoes an analogous process of ripening, which has been studied very carefully, and from its theoretical interest has
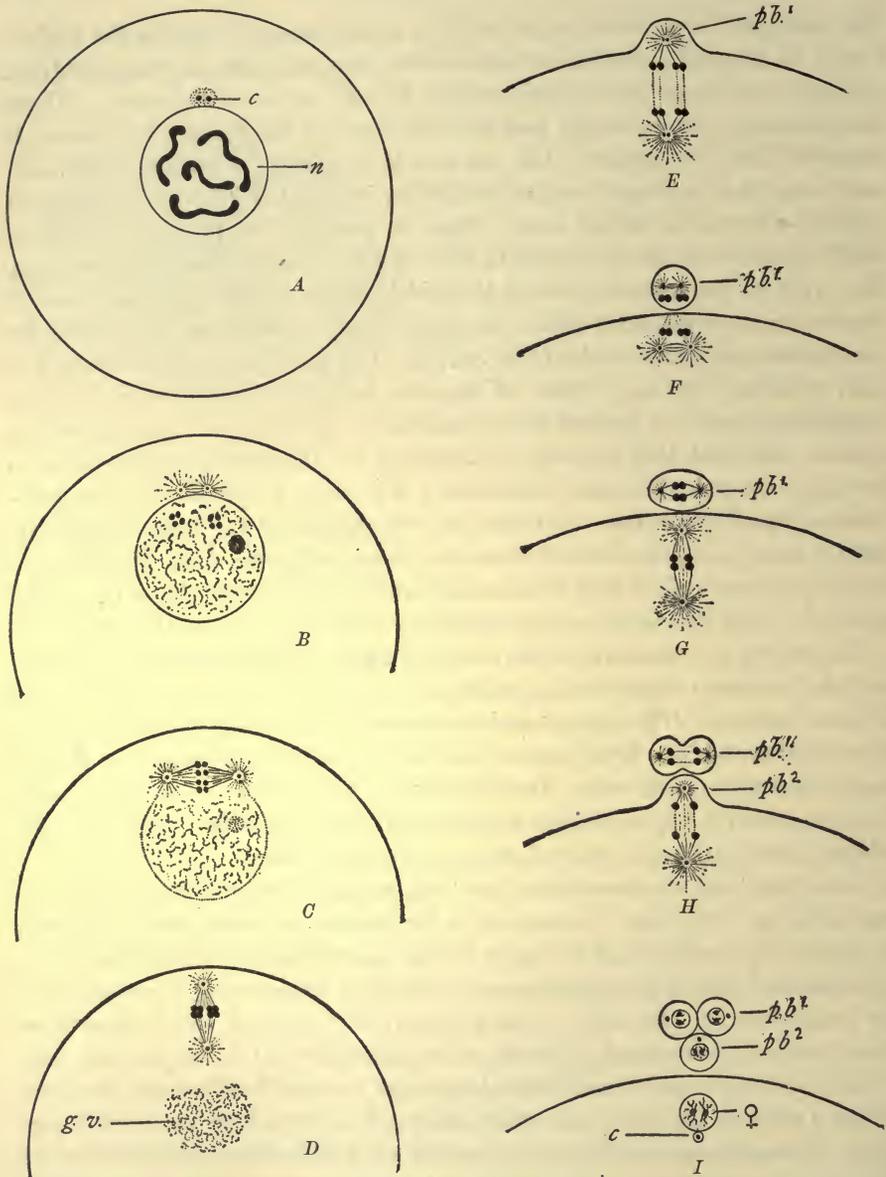
FIG. 308.—Stages in the maturation of the ovum; diagrammatic (mainly from Wilson): A, the original ovarian ovum; n, its nucleus, containing four chromosomes; c, its double centrosome, surrounded by the attraction sphere; in B much of the chromatin has begun to degenerate; the rest has become arranged into two quadruple groups of chromosomes, or tetrads; the formation of the spindle and the asters has begun; in C the first polar amphiaster, bearing the chromosomes, is completed; in D the amphiaster has become rotated and has travelled toward the surface of the ovum; $g. v$, the degenerated remains of the nucleus; in E the division of the tetrads into double groups of chromosomes, or dyads, has begun, and the first polar body, $p. b^1$, is indicated; in F the first polar body, containing two dyads, has been extruded; the formation of the second polar amphiaster has begun; in G the first polar body is preparing to divide; the second polar amphiaster is fully formed; in H the division of the dyads into single chromosomes in both the first polar body and the egg has begun, and the second polar body, $p. b^2$, is indicated; in I the formation of the polar bodies is completed; ♀, the egg-nucleus, containing two small chromosomes, one-half the original number. In fertilization the spermatozoon will bring in two additional chromosomes, thus restoring the total number of four.

given rise to a large amount of discussion. Maturation occurs approximately as the ovum is leaving the ovary, the exact time-relations being not yet determined. It consists of a karyokinetic division of the nucleus, essentially like karyokinesis (mitosis) in ordinary cell-division, and an expulsion of one portion from the cell. This occurs twice in succession. The cast-off bits of protoplasm are known as *polar bodies.* The details of the process of maturation are as follows (Fig. 308): The nucleus of the original ovarian ovum contains the same number of chromosomes as the ordinary tissue-cells (A). At the beginning of maturation much of the chromatic substance begins to degenerate, and later it disappears wholly (B, C, D). The remainder is rearranged into groups of chromosomes, usually four in each group, which is called a " quadruple-group " or " tetrad " (B). The number of tetrads is always one-half the number of original chromosomes, while the total number of chromosomes in the nucleus at this stage is double the original number. The nucleus moves from its position in the interior of the egg toward the surface, and the nuclear membrane begins to disappear. At the same time the two minute cytoplasmic structures, the centrosomes, which lie close beside the nucleus, separate and take up positions at a considerable distance apart from each other, in some cases even upon opposite sides of the nucleus. The substance lying between them—either the cytoplasmic network or the achromatic substance of the nucleus—loses its reticular appearance, becomes filamentous, and arranges itself in the form of a spindle with the threads extending from pole to pole (C, D). The groups of chromosomes become attached to the spindle threads midway between the poles. At each pole lies a centrosome, and about it the cytoplasm becomes arranged in the form of a star, the *aster.* The spindle with the two asters is known as the *polar amphiaster,* and the complicated structure seems to be formed, as in ordinary cell-division, for the sole purpose of dividing the nucleus into two portions. This is now performed (E); each quadruple-group of chromosomes splits into two, and these, known as " double-groups," or " dyads," are drawn apart from each other and toward the spindle poles, probably by contraction of the fibres of the spindle. The nucleus is thus divided into halves. While the division has been proceeding, the spindle has wandered halfway outside the egg, and, when it is completed, one of the resulting nuclear halves, comprising one-half of the full number of dyads, together with the centrosome and the aster, finds itself entirely extruded from the egg and lying within the perivitelline space. It is known as the *first polar body* ($F, p. b^1$). The diminished nucleus within the ovum proceeds at once to undergo a second karyokinetic division similar to the first (G, H, I); each of the remaining dyads divides into two single chromosomes, which are pulled apart from each other; and a *second polar body* ($p. b^2$), containing one-half the number of single chromosomes characteristic of the tissue-cells, is extruded. Apparently the two polar bodies are of no further use. In many animals the first divides into two, but sooner or later both degenerate and disappear. The remnant of the nucleus left within the egg, much reduced in size, wanders back to the interior. Its chromosomes, reduced to one-half the number

belonging to the ovarian ovum, are resolved again into scattered chromatic substance.   It develops a membrane and becomes again a resting nucleus.   It is known henceforth as the *egg-nucleus*, or *female pronucleus*, and it awaits the coming of the male.   Its centrosome gradually degenerates and disappears.

Thus the curious process of maturation of the ovum is different in detail from that of maturation of the spermatozoon.   In the latter the primary spermatocyte divides into four functional spermatozoa; in the former the primary ovocyte divides into two functionless polar bodies (or, by subdivision of the first, three, which have been called abortive eggs) and one functional ovum. It is entirely probable, however, that the essence of the process is exactly the same in the two cases, and lies in the reduction of the chromatic substance of the nucleus.   Van Beneden found in *Ascaris* that in the maturation of the ovum, as in that of the spermatozoon already referred to, the number of chromosomes is halved and that the number in the two germ-cells is the same. This has since been proved abundantly in other forms, as well as the further associated fact that the mature germ-cells contain each one-half the number of chromosomes that are characteristic of the somatic cells; it is wholly probable that these facts are universal in sexual reproduction.   Each mature germ-cell, therefore, while in reality a cell, is, when compared with the somatic cells, incomplete.   The subsequent union of the two in fertilization restores the chromosomes to their normal number.   Inasmuch as the chromatin is probably the all-important constituent of the germ-cells, the bearer of the paternal and the maternal inherited characteristics, the phenomena of maturation are of great interest.   Most biologists follow Hertwig and Weismann in regarding maturation as an adaptation for the prevention of the constant increase in quantity of the hereditary substance that would otherwise take place with every union of ovum and spermatozoon.   Without a reducing process the quantity of chromatin in cells would become in a very few generations inconveniently great.   Maturation is a preparation of each germ-cell for union with its mate.

The Ovary; Ovulation.—The ovaries (Fig. 309, *o*) are often spoken of as glands, but they are not glands according to the ordinary histological and physiological use of the term.   They are solid organs with a structure peculiar to themselves, and their function is the production of ova.   Their stroma consists of fine connective tissue with numerous connective-tissue cells.   The ova are developed in the interior within cavities called, from their discoverer, *Graafian follicles* (*G.f*), from primitive ova that are modified cells of the germinal epithelium of the embryo.   It has been calculated that the two human ovaries at the age of eighteen years contain an average of 72,000 primitive ova, but that not more than four hundred of these arrive at maturity.   Each Graafian follicle is lined by an epithelial layer several cells thick, the *membrana granulosa,* and is filled with clear viscid fluid, the *liquor folliculi,* which contains albuminoid matter.   Imbedded in the epithelium upon one side is usually a single ovum, completely surrounded by the cells and forming a prominent hillock which projects well into the cavity of the follicle.   The

epithelium immediately surrounding the ovum is the *discus proligerus.* Within the discus the ovum grows and becomes surrounded by the *zona pellucida.* In the process of growth the Graafian follicle approaches the surface of the ovary,
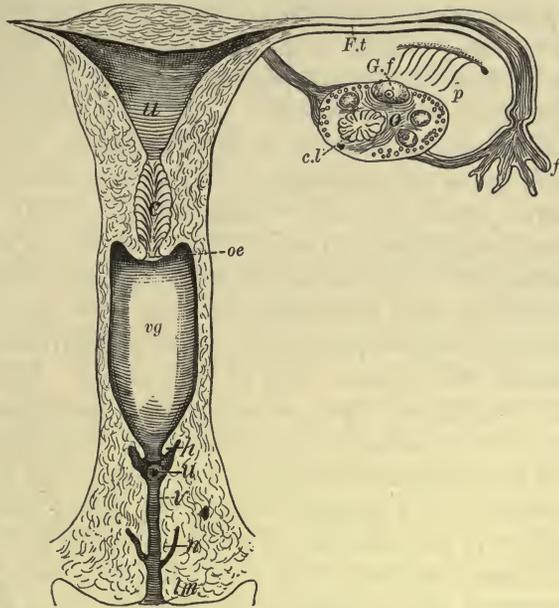
FIG. 309.—Diagram of the female reproductive organs (modified from Henle and Symington): *o*, ovary; *G.f*, Graafian follicle containing an ovum; *c.l*, corpus luteum; *p*, parovarium; *f*, fimbriated end of *F.t*, Fallopian tube; *u*, body, and *c*, cervix of uterus; *o.e*, os uteri externum; *vg*, vagina; *h*, hymen; *u*, opening of urethra; *v*, vulval cleft; *n*, labia minora, or nymphæ; *l.m*, labia majora.

and finally comes to form a minute rounded vesicular projection covered only by the ovarian epithelium. When fully ready for discharge, the wall of the follicle becomes ruptured, probably by the increasing pressure of the contained liquid, and the ovum with its *zona pellucida* and a portion or all of the *discus proligerus*, now called the *corona radiata,* is cast out upon the surface of the ovary to be taken up by the Fallopian tube. The empty follicle undergoes changes and becomes the *corpus luteum* (*c.l*). Usually the *corpus luteum* degenerates within a few days and ultimately disappears. If, however, pregnancy follows ovulation, it grows very large, perhaps because of the congested state of the reproductive organs, and remains for months before the retrograde metamorphosis sets in. Not all Graafian follicles reach maturity and burst, for many, after developing to a considerable size, undergo degenerative changes, characterized by liquefaction and disappearance of their contents.

The discharge of the ovum is known technically as *ovulation.* In most animals ovulation is a periodic phenomenon accompanying certain seasons, and is marked by general sexual activity. In woman and many domesticated animals the relation to the seasons no longer exists, but too little is known of the causes and time-relations of the phenomenon and its general bearings upon other physiological processes, notably upon menstruation in woman. A large

but not wholly decisive literature upon the subject in the human being has been written. It is a common belief, originating in the seventeenth century, that ovulation in woman is a periodic phenomenon occurring regularly every month and contemporaneous with the occurrence of the menstrual flow, and numerous post-mortem observations of the presence in the ovary of freshly-discharged Graafian follicles at the menstrual period afford evidence of the frequent coincidence of the two phenomena. But ovulation at the time of menstruation, though probably usual, is not exclusive of ovulation at other times, for intermenstrual observations of fresh ovarian scars are not rare, and prove without doubt that discharge of an ovum may occur at any time between two successive periods (see under Menstruation, p. 895). Graafian follicles develop even during infancy; most of them, and perhaps all, retrograde without discharging their ova, but the occasional instances of pregnancy at the ages of seven, eight, or nine, prove that ovulation may occur during childhood. Ovulation usually begins at puberty, its commencement thus coinciding with that of menstruation, and continues until the climacteric. After the climacteric it may occur in exceptional cases, although here, as before puberty, retrogressive degeneration of the Graafian follicles is the rule. It is commonly believed that ovulation is at a standstill during both pregnancy and lactation. The undoubted possibility of a pregnancy originating during lactation would, however, seem to prove the possibility of ovulation during the latter period. It is not decided whether removal of the uterus does away wholly with ovulation.

The Fallopian Tube.—Each of the *Fallopian tubes* (Fig. 309, *F. t*), or *oviducts*, opens into the peritoneal cavity about one inch from the corresponding ovary. Around the opening is an expanded fringe of irregular processes, the *fimbriæ* (*f*), one of which is attached to the ovary. The length of the tube is between three and four inches, and the opening into the uterus is extremely small. The chief structures in the walls of the oviducts that are of physiological interest are the double layer of plain muscle, an outer longitudinal and an inner circular coat, longitudinal fibres from which pass also into the fimbriæ; and the cilia with which the tube is lined throughout, and which are present also upon the inner side of the fimbriæ. The direction of the ciliary movement is from the ovary toward the uterus. The primary function of the Fallopian tubes is to convey ova from the ovary to the uterus; they also convey spermatozoa in the reverse direction; and within them the union of ovum and spermatozoon usually takes place.

The mechanism of the receipt of the ovum by the tube is not fully understood. After ovulation the ovum is slightly adherent to the surface of the ovary by the agency of the viscid *liquor folliculi*. It is possible, but it has not been proved, that in the human being, as has been seen in some animals, the expanded, fimbriated end of the Fallopian tube clasps the ovary when the egg is discharged. The passage of the ovum into the tube is probably brought about by the cilia lining the fimbriæ. Once within the tube, the ciliary action, assisted perhaps by contraction of the muscular fibres in the walls, carries the ovum slowly along toward and finally into the uterus. In

some mammals the passage occupies three to five days; the time in woman is not known.

The Uterus.—The *uterus* (Fig. 309, *u*), or *womb*, receives the ovum from the Fallopian tube and passes it on, if unimpregnated, to the vagina; on the other hand, it receives from the vagina spermatozoa and transmits them to the Fallopian tubes; it is the seat of the function of menstruation; when impregnation has taken place, it retains and nourishes the growing embryo, and ultimately expels the child from the body. Its structure accords with these functions. Its thick walls consist largely of plain muscular tissue arranged roughly in the form of three indistinctly marked layers. Of these, the external and the middle coats are thin; the fibres of the former are arranged in general longitudinally, those of the latter more circularly and obliquely. The third, most internal layer, which is regarded by some as a greatly hypertrophied muscularis mucosæ, forms the greater part of the uterine wall. Its fibres are arranged chiefly circularly; toward the upper part they become transverse to the Fallopian tubes, and at the cervix longitudinal fibres lie within the circular ones. The individuality of the muscular layers and uniformity in the course of the fibres is largely interfered with by the numerous blood-vessels of the uterine walls. The uterus is lined by an epithelium composed of columnar ciliated cells, except in the lower half of the cervix, where a stratified non-ciliated epithelium exists. The direction of the ciliary movement in woman is not definitely known; in other mammals the cilia appear to sweep toward the *os uteri.* The mucous membrane is thick, and contains very numerous branching tubular glands that are lined by ciliated epithelium and have a tortuous course, terminating in the edge of the muscular layer. They secrete a viscid mucous fluid. Between the glands are branched connective-tissue cells that are not unlike the connective-tissue cells of embryonic structures, and wandering cells. Lymph-spaces and blood-capillaries exist. The development of the tissue goes on slowly up to the time of puberty, and, as we shall see, after puberty the mucous membrane is subject to constant change.

Menstruation.—Except during pregnancy the most striking activities of the uterus are associated with that peculiar female function which, from its monthly periodicity, is called *menstruation.* The most obvious external fact of this phenomenon is the discharge every month of a bloody, mucous fluid through the vagina; the most obvious internal facts are the bleeding and the degeneration and disappearance of a portion of the mucous membrane of the body of the uterus. This curious process, though having analogies in lower animals, occurs most markedly in the human female, and from before the time of Aristotle to the present, among both primitive and civilized races, its significance has been the cause of much speculation. The detailed phenomena of menstruation are not as well known as they should be. Experimentation is practically out of the question, and the opportunities of careful post-mortem study of normal healthy uteri at different stages are rare. The main facts are as follows:

Some days before the flow occurs the mucous membrane of the body of the uterus begins to thicken, partly by an active growth of its connective tissue elements and partly by an excessive filling of its capillaries and veins with blood. The cause of this swelling is not known. It continues until the membrane has doubled or trebled in thickness, and, according to some authorities, the uterine cavity becomes a mere slit between the walls. Then occurs an infiltration of blood-corpuscles and plasma, probably largely by diapedesis, although possibly assisted by rupture, through the walls of the swollen capillaries into the connective-tissue spaces beneath the epithelial lining of the uterine wall. The epithelium is thus pressed up from beneath, and begins rapidly to undergo disintegration (perhaps fatty degeneration) and to disappear. The immediate cause of the degeneration is not definitely known. The connective-tissue elements and the upper portion of the glands are involved in the degenerative change. The capillaries, thus laid bare, burst, and the dark blood oozes forth and, mixed with disintegrated remains of the uterine tissues, with the mucous secretion of the uterus and the vagina, and with the escaped lymph, passes away, drop by drop, from the body. There is great difference of opinion as to the extent of the destruction of uterine tissue. On the one extreme side are those who claim that the loss of tissue is normally wholly trivial and secondary, the hyperæmia and the bloody glandular discharge being the important events. Other authorities, equally extreme, have observed a disappearance of the whole mucous membrane except the deepest layers containing the bases of the glands; this is probably pathological. From all the evidence an opinion intermediate between these two views seems most reasonable—namely, that usually and physiologically only the superficial portion of the mucous membrane disintegrates. Differences in the amount undoubtedly occur. Occasionally it happens that the membrane, instead of disintegrating, comes away in pieces of considerable size. The term *decidua menstrualis* is applied to the lost coat. The flow continues upon an average four days or more. From observations upon 2080 American women Emmet[1] finds the average duration of the flow at puberty to be 4.82 days, the average in later life 4.66 days. The amount of blood discharged can be determined only with great difficulty. It probably varies greatly, but is commonly estimated at from 100 to 200 cubic centimeters (4–5 ounces). The blood is slimy, with abundant mucus; usually it does not coagulate. Epithelium cells, red corpuscles, leucocytes, and detritus from the disintegrated tissues, occur in it, and it has a characteristic odor. As the flow ceases, a new growth, of connective-tissue cells, capillaries, glands, and from the glands superficial epithelium, begins, and the mucous membrane is restored to its original amount. Whether a resting period follows before the succeeding tumefaction occurs, is not definitely known, but it seems probable. The durations of the various steps in the uterine changes are not well known, and probably vary in individual cases. Minot[2] suggests the following approximate times:

[1] T. A. Emmet: *The Principles and Practice of Gynæcology*, 2d ed., 1880.
[2] C. S. Minot: *Human Embryology*, 1892.

Tumefaction of the mucosa, with accompanying structural changes . . . . . 5 days.
Menstruation proper . . . . 4 "
Restoration of the resting mucosa . . . . 7 "
Resting period . . . . 12 "
_____
Total . . . . 28 days.

The menstrual changes in the uterus are accompanied by characteristic phenomena in other parts of the body. The Fallopian tubes are congested, and, according to some authorities, their mucous membrane degenerates and bleeds like that of the uterus. The ovaries are likewise congested. As has been stated, it is commonly believed, but not definitely proved, that ovulation accompanies each period. Frequent accompaniments are turgescence of the breasts, swelling of the thyroid and the parotid glands and the tonsils, congestion of the skin, dull complexion, tendency toward the development of pigment, and dark rings about the eyes. The skin and the breath may have a characteristic odor. In singers the voice is often impaired, which is one instance of a general nervous and muscular enervation. Mental depression often exists. In most cases sexual instincts do not appear to be heightened. Pain is a frequent accompaniment, and nervous and congestive pathological phenomena may, at times, become very pronounced. Recent work has shown that the various phenomena accompanying menstruation are evidences of a profound physiological change, with a monthly periodicity, that the female human organism undergoes, and of which the uterine changes are only a part. Thus, during the intermenstrual period there is a gradual increase of nervous tension and general mobility, of vascular tension manifested by turgescence of the blood-vessels, a gradual increase of nutritive activity manifested by increased production and excretion of urea and increased temperature, and a gradual increase of the heart's action in strength and rate.[1] These various activities of the organism usually attain a maximum a few days before the menstrual flow begins and then undergo a rapid fall, which reaches a minimum toward the close of the flow; a second lesser maximum may occur a few days after the flow ceases. All organic activities that have been carefully investigated show evidences of such a monthly rhythm. It is not known that the male possesses such a period.

The first menstruation is usually regarded as the index of the oncoming of puberty or sexual maturity, and in temperate climates occurs usually at the age of fourteen to seventeen. Its onset is earlier in warm than in cold climates, in city than in country girls, and varies in time with food, growth, and environment. Exceptionally menstruation may begin in infancy or later than puberty, and it has even been known to be wholly wanting in otherwise normal women. Normally, it ceases during pregnancy, and probably usually during lactation, although there are frequent exceptions to the latter rule. Complete removal of the ovaries appears to put an entire end to menstruation. Its final cessation,

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[1] *Cf.* Mary Putnam Jacobi : "The Question of Rest for Women during Menstruation," *Boylston Prize Essay,* 1876 ; C. Reinl: *Sammlung klinische Vorträge,* No. 243, 1884 ; O. Ott : *Nouvelles archives d'obstétrique et de gynécologie,* v., 1890.

which is a gradual process extending over several months, usually marks the climacteric (menopause) or end of the sexual life, and occurs usually at the age of forty-four to forty-seven. Exceptionally the flow may cease early in life or extend to extreme old age.

Comparative Physiology of Menstruation.—The comparative physiology of menstruation, although it has been studied only incompletely in a few domesticated animals and some monkeys,[1] sheds some valuable light upon the phenomenon in woman. In animals lower than man, in a wild state, the desire and power of reproduction are usually limited to seasonal periods. At such times conception is possible, and probably usually takes place. Such periods are known as "rut," "heat," and "œstrus." During the rest of the year sexual activities are in abeyance. Domestication, with its artificial conditions of regular food-supply, warmth, and care, has increased productiveness (Darwin) and rendered the reproductive periods more frequent. If impregnation be prevented, as is often the case in domesticated animals, the periods of "heat" appear with great frequency and regularity (monkey, mare, buffalo, zebra, hippopotamus, four weeks; cow, three weeks; sow, fifteen to eighteen days; sheep, two weeks; bitch, nine to ten days.) They are characterized by general nervous excitement, desire and power of conception, congestion and swelling of the external genital organs, and a uterine discharge. The latter is scanty, mucous, and bloody, the amount of blood increasing in ascending the evolutionary scale. The histological processes occurring in the uterus have been studied carefully by Retterer in the dog and by Heape in the monkey. In the latter the processes seem to be nearly identical with those of man. In the dog, growth and congestion of the mucosa occur, and are followed by rupture of the capillaries, extravasation of blood, and degeneration of the tissues, but it is doubtful whether the epithelium is actually shed. It is generally believed that "heat" in the lower mammals is accompanied by ovulation. It is not necessarily so in monkeys. The phenomena of "heat" are thus closely similar to those of human menstruation, the similarity being most marked in the monkeys. In addition to these more hidden phenomena there is present sexual desire, which in the human female is largely absent at such periods.

Theory of Menstruation.—The significance of menstruation is in great dispute. All modern theories agree in regarding it as associated in some way with the function of childbearing. The flow was early believed to be a means employed by the body to get rid of a plethora of nutriment. This was followed by the well-known hypothesis, put forward especially by Pflüger (1865), and even now widely accepted. According to this hypothesis,[2] the menstrual bleeding and the uterine denudation occur for the purpose of providing a fresh uterine surface to which the egg, if impregnated, can readily attach itself, just as, in grafting, the gardener provides a wounded surface upon which the young

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[1] *Cf.* A. Wiltshire : *British Medical Journal*, March, 1883; E. Retterer : *Comptes rendus des séances et mémoires de la Société de biologie*, 1892; W. Heape : *Philosophical Transactions of the Royal Society* (B). vol. 185, pt. i., 1894.

[2] E. F. W. Pflüger : *Untersuchungen aus dem physiologischen Laboratorium zum Bonn*, 1865.

scion is set, or, in uniting two membrane-covered tissues, the surgeon first wounds or freshens their surfaces. The mechanism of this uterine process is as follows : The constant growth of the ovarian cells and the consequent swelling of the ovary subject the ovarian nerve-fibres, and through them the spinal cord, to a constant slight stimulation. Through the summation of the stimuli within the cord a reflex dilatation of the vessels in the genital organs is produced. The excessive blood-supply leads in turn to the tumefaction of the uterus, and frequently to the ripening of a Graafian follicle. The bleeding follows, and at the same time or slightly later the rupture of the follicle occurs, provided the latter be sufficiently advanced in growth. The menstrual flow and ovulation are, therefore, two phenomena conditioned usually by the same cause, namely, the menstrual congestion, yet either may occur without the other. Pflüger's hypothesis accounts clearly for the absence of menstruation after removal of the ovaries. Numerous other theories have been proposed, no one of which can be said to be widely and generally accepted. The present tendency in belief is as follows : Ovulation and menstruation are in great part independent phenomena ; they may or they may not coexist ; the uterine growth is a preparation for the future embryo ; the tissue of the *decidua menstrualis* is the forerunner of the *decidua graviditatis* (p. 909) ; if an ovum, whenever it is discharged, be fertilized, it attaches itself to the thickened uterine wall, the tissues become the *decidua graviditatis,* pregnancy follows, and the *decidua* is not discharged until the time of parturition ; if, however, fertilization does not take place, there is no attachment, the tissues degenerate and become the *decidua menstrualis,* and the flow occurs. The suggestion of Jacobi[1] is not an extreme one : " The menstrual crisis is the physiological homologue of parturition." Its monthly periodicity is not explained. Regarding its mechanism the above hypothesis of Pflüger, although not yet proven experimentally, seems not unreasonable.

The mystery of menstruation largely ceases when we recognize what is undoubtedly a fact, that the phenomenon is a highly developed inheritance from our mammalian ancestors, and that, although in the human race under the influence of civilization and social life it has largely lost its technical sexual significance, it is, nevertheless, primarily a reproductive phenomenon derived directly from the lower females. Nature has endowed the latter, in a manner yet unknown, with reproductive periods that are pronounced in the wild state and are coincident with certain of the seasons. A primitive seasonal period may perhaps still be shown in woman by the greater proportion of births that take place during the winter months than at other times of the year : this signifies greater sexual activity during the months of spring, as is the case in most animals.[2]

[1] Mary Putnam Jacobi : *American Journal of Obstetrics,* xviii., 1885.

[2] " The largest number [of human births] almost always falls in the month of February, ... corresponding to conceptions in May and June. .... Observations tend to show the largest number of conceptions in Sweden falling in June ; in Holland and France, in May–June ; in Spain, Austria, and Italy, in May ; in Greece, in April. That is, the farther south the earlier the spring and the earlier the conceptions."—Mayo-Smith : *Statistics and Sociology,* 1895.

Domestication has, however, interfered with the original plan of nature. It has rendered the lower forms more prolific and has made more frequent their reproductive periods. Civilization has done exactly the same for woman. It has rendered her more prolific and has made more frequent her reproductive periods. It is wholly probable that the menstrual periods of woman are the homologues of the frequent reproductive periods of the lower forms. It has been seen that the latter are characterized by the same kind of phenomena that exist in the former; the characteristic human menstrual phenomena are least developed in the lower mammals, much more so in the monkey, and are most pronounced in the human female. For what purpose this evolution of function has taken place we do not know. Below the human species conception is confined to these times of "heat;" in woman it is possible at other than her menstrual periods. In this respect woman is more highly endowed than her mammalian ancestors.

The Vagina.—The *vagina* (Fig. 309, *vg*) is the broad passage from the uterus to the external organs. Its walls consist of smooth muscle fibres, arranged both circularly and longitudinally. It is lined by stratified scaly epithelium and is surrounded by erectile tissue. Its walls contain few glands. Its specific functions are connected solely with the reproductive process; in copulation it receives the penis and the semen. Its cavity is the pathway outward for the products of menstruation and, in parturition, for the child.

The Vulva and its Parts.—The *vulva* (Fig. 309) comprises the genital organs that are visible externally—viz. the *mons Veneris*, the *labia majora (l.m)*, the *labia minora* or *nymphœ* (*n*), the *clitoris*, which is the diminutive homologue of the penis of the male, and the *hymen* (*h*), or perforated curtain that guards the entrance to the vagina and is usually ruptured at the time of the first coition. The vulva receives the openings of the vagina, the urethra (*u*), and the ducts of Bartholini's glands. Its parts are capable of turgidity through its rich vascular supply, and perform minor ill-defined, adaptive, and stimulating functions in copulation. Their surface is covered by mucous membrane which is moistened and lubricated by a secretion from numerous mucous follicles, sebaceous glands, and the glands of Bartholini. The latter are comparable to Cowper's glands of the male and secrete a viscid fluid.

The Mammary Glands.—The mammary glands, being active only during the period of lactation, may best be studied in connection with that function (see p. 201).

Internal Secretion.—*A priori*, the reproductive organs can scarcely be regarded as organs that are quiescent during the greater part of life and passively await the reproductive act. The view that they are more than this is supported by some, although slight, experimental evidence. Notwithstanding the fact that removal of the testis or the ovary in adult life is often unaccompanied by great somatic changes, the profound effects of early castration upon development, in both the male and female, show that upon the presence of the sexual organs depends the appearance of many of the secondary sexual characters—characters which apparently are independent of those organs, and yet

of themselves distinguish the individual as specifically masculine or feminine. The mode of dynamic reaction of the sexual organs upon the other organs can at present be little more than hinted at. It is entirely probable that such reaction is either nervous or chemical, or perhaps it is both combined. Regarding the former little is known. Regarding the latter, recent assertions of the general invigorating effects of injections of testicular extracts in the adult, although in most cases not founded upon careful experimentation, are, nevertheless, suggestive, and point to a possible normal and constant contribution of specific material by the reproductive glands to the blood or lymph, and thus to the whole body. Such a process is spoken of as *internal secretion,* and in the case of the thymus and thyroid glands its occurrence seems undoubted (p. 205). As to the reproductive organs, investigation of the subject is yet in its mere infancy, and it is too early to say with any degree of authority what the truth of the matter is. Very recently Zoth[1] has shown that daily injections of testicular extract during one week increased by 50 per cent. the working power of a man's neuro-muscular system. The increase manifested itself both by lessened susceptibility to fatigue and, in a still higher degree during the periods of rest from labor, by increased power of recovery. What part of the whole neuro-muscular system is affected by the specific substance is not decided.

D. The Reproductive Process.

Attention has heretofore been given to the general functions of the reproductive organs. We come now to the special phenomena connected with the reproductive process itself, and have to trace the history of the spermatozoon, the ovum, and the embryo. It should be borne clearly in mind that the essential part of the reproductive process is the fusion of the nuclei of the two germ-cells. Investigation is making it more and more probable that the spermatozoon and the ovum, although so different in appearance and general behavior, are fundamentally and in origin both morphologically and physiologically equivalent cells. In the processes of their growth and maturation they are secondarily modified, the one into an active locomotive body, the other into a passive nutritive body. The modifications in both are confined, however, to the cell-protoplasm (cytoplasm and centrosome) ; the essential parts, the nuclei, remain unmodified and both morphologically and physiologically equivalent down to the time of their fusion in the process of fertilization. The many and complex details of the reproductive process exist for the sole purpose of bringing together these two minute masses of chromatin.[2]

Copulation.—Copulation is the act of sexual union, and has for its object the transference of the semen from the genital passages of the male to those of the female. It is preceded by erection of the penis and turgidity of the organs of the vulva. These latter occurrences are in the main vascular phenomena,

[1] O. Zoth: *Pflüger's Archiv für die gesammte Physiologie,* lxii., 1896.

[2] Compare Th. Boveri : " Befruchtung," Merkel und Bonnet's *Ergebnisse der Anatomie und Entwickelungsgeschichte,* i., 1892.

and are brought about by a distention of the cavernous spaces of the erectile tissues with blood. The vascular phenomena are, however, accompanied by complex nervous and muscular activities. As regards the penis, the arteries supplying the organ relax and allow blood to flow in quantity to the *corpora cavernosa* and the *corpus spongiosum.* Simultaneous relaxation of the smooth muscle fibres scattered throughout the trabecular framework of the corpora increases the capacity of the blood-spaces. Furthermore, the *ischio-cavernosus* (*erector penis*) and *bulbo-cavernosus* muscles contract and compress the proximal or bulbous ends of the corpora and the outgoing veins. The result of this combined muscular relaxation and contraction is a free entrance of blood into and a difficult exit from the vascular spaces; this leads to a swelling and distention which aid further in compressing the venous outlets and, being limited by the tough, fibrous tunics of the corpora, result in making the organ stiff, hard, erect in position, and well adapted to its specific function. During the process of erection the cresta of the urethra or *caput gallinaginis*, which is an elevation extending from the cavity of the bladder into the prostatic portion of the urethra and containing erectile tissue, becomes turgid and, by the aid of the contraction of the *sphincter urethræ*, effectually closes the passage into the bladder. Erection is a complex reflex act, the centre of which lies in the lumbar spinal cord and may be aroused to activity by nervous impulses coming from different directions. Impulses may originate in the walls of the ducts of the testis from the pressure of the contained semen or in the penis from external stimulation of the nerve-endings in the skin, in both cases passing along the sensory nerves of the organs to the spinal centre; or they may originate in the brain and pass downward through the cord, the impulses in this case corresponding to sexual emotions. The centrifugal paths for the arteries are along the *nervi erigentes*, which are true vaso-dilator nerves, and in the mammals, where experiment has proved their existence, pass from the spinal cord along the posterior lumbar (monkey) or anterior sacral (monkey, dog, cat) nerves to their arterial distribution. The *ischio-* and *bulbo-cavernosus* muscles are under the control of their motor nerve supply, consisting of branches of the perineal nerve.

In the female, anatomists recognize the homologues of the male erectile parts as follows: the *clitoris* with its *corpora cavernosa* and *glans* as the homologue of the penis, the two *bulbi vestibuli* as that of the bulb of the *corpus spongiosum*, the *pars intermedia* perhaps as that of the *corpus spongiosum* itself, and the *erector clitoridis* muscle as the homologue of the *erector penis* (*ischio-cavernosus*). The mechanism of erection is similar to that in the male, and the result is a considerable degree of firmness in the external genital organs.

The sexual excitement attendant upon copulation is usually much greater in man than in woman, and culminates in the sexual orgasm, when the emission of semen from the penis into the vagina occurs. It will be remembered that the prepared semen is stored in the ducts of the testes. The discharge of the fluid is a muscular act which begins probably in the *vasa efferentia*

and the canal of the *epididymis*, and sweeps along the powerful muscular walls of the *vasa deferentia* in the form of a series of peristaltic waves. The seminal vesicles also contract, and the mixed fluid and spermatozoa are poured through the ejaculatory ducts into the prostatic portion of the urethra. The muscles of the prostate expel the prostatic fluid and help to pass the semen onward. The glands of Cowper possibly add their contribution. But the final urethral discharge is effected especially by powerful rhythmic contractions of the already partially contracted striped muscles, viz. the *ischio-* and *bulbo-cavernosi*, the *constrictor urethræ*, and probably the anal muscles, the result of the complex series of actions being to expel the semen with some force into the upper part of the vagina close to the *os uteri*. Ejaculation is a reflex act. The centre lies in the lumbar spinal cord; the centripetal nerves are the sensory nerves of the penis, stimulation of the glans being especially effective; the centrifugal nerves are the nerves to the various muscles. In the female during ejaculation the glands of Bartholini pour out a mucous fluid upon the vulva. There is possibly a downward movement of the uterus, brought about by contraction of its round ligaments and accompanied perhaps by a contraction of the uterine walls themselves. But all muscular and erectile activity, as well as sexual passion, is less pronounced in woman than in man.

Locomotion of the Spermatozoa.—The union of the spermatozoon and the ovum probably takes place usually in the Fallopian tube not far from its ovarian end, and to this place the spermatozoa at once proceed. Their mode of entrance into the uterus is not wholly clear; it is quite generally believed, but without conclusive experimental proof, that relaxation of the uterus immediately after copulation exerts a suction upon the fluid which aids in its passage through the os and the cervix. It is possible that active contraction of the vaginal walls assists. However these may be, the main agency in the locomotion of the spermatozoa through the body of the uterus and the Fallopian tubes, and probably also from the vagina into the uterus, is the spontaneous movement of the spermatozoa themselves. By the lashing of their tails they wriggle their way over the moist surface, being stimulated to lively activity probably by the opposing ciliary movements in the epithelium lining the passages. Kraft[1] has shown in the rabbit that, when spermatozoa in feeble motion are placed upon the inner surface of the oviduct, not only are they thrown into active contractions, but they move against the ciliary movement, *i. e.* up the oviduct. The capacity of the male cells thus to respond by locomotion in the opposite direction to the stimulating influence of the ciliary cells over which they have to pass, is an interesting adaptation. Probably this is the directive agency that enables the spermatozoa to follow the right path to the ovum, while the ovum, being in itself passive, is by the same ciliary movement brought toward the active male cell. The time occupied in the passage of the spermatozoa is unknown in the human female, but is probably short; in the rabbit spermatozoa have been known to reach the ovary within two and three-quarter hours after copulation. As has been seen, spermatozoa are probably capable of living

[1] H. Kraft: *Pflüger's Archiv für die gesammte Physiologie*, xlvii., 1890.

within the genital passages for several days, when, if ovulation has not taken place, they perish. If, however, an ovum appears, they at once approach and surround it in great numbers, being apparently attracted to it in some mysterious manner. The work of Pfeffer,[1] who found that in the fertilization of ferns malic acid within the female organs attracts the spermatozoids to their vicinity, suggests strongly that also among animals the attraction may be a chemical one, the ovum containing or producing something for which the spermatozoon has an affinity. If so, the meeting of the two germ-cells is an illustration of a widespread principle of nature known as *chemotropism*, or *chemotaxis*. Experimental evidence upon the subject in animals is wanting.

Fertilization.—It will be remembered that the ovum and the spermatozoon undergo in their growth the process of maturation, and that this process consists essentially of a loss of one-half of the chromosomes of their nuclei. The germ-cells thus matured meet, as we have seen, in the distal half of the Fallopian tube and fuse into one cell, the process of fusion being called *fertilization* or *impregnation*. The details of fertilization have not been observed in the case of the human being, and the following account is generalized from our knowledge of the process in other mammals and lower animals. In its broad outlines fertilization is probably the same in all animals, the differences being confined to details.

The ovum at the time of fertilization is surrounded by the *zona radiata* alone, the *corona radiata* having been lost. The spermatozoa swarm about the *zona*, lashing their tails and attempting to worm their way through it. Several may succeed in reaching the perivitelline space, but for some unknown reason in most cases one only penetrates the substance of the ovum; the others ultimately perish. In mammalian ova there is no micropyle, and apparently the successful spermatozoon may enter at any point, the protoplasm of the egg rising up as a slight protuberance to meet it (Fig. 310, *c*). In some animals the tail is left outside to perish; in others it enters, but then disappears; in no case does it appear to be of further use. The head and probably the middle-piece are of vital importance. The head, now known as the *sperm-nucleus* or *male pronucleus*, proceeds by an unknown method of locomotion toward the centre of the egg, and becomes enlarged by the imbibition of fluid (Fig. 310, B, *s*). The matured nucleus of the ovum, or *egg-nucleus* (*e*), remains in the resting stage from the time of maturation until the entrance of the sperm. Then, without changing its character, it moves slowly toward the future meeting-place of the two nuclei, which is near the centre of the egg. The sperm-nucleus finally reaches the egg-nucleus (Fig. 311, c), its chromatin enters into the latter, and the two fuse together to form a new and complete nucleus, called the *first segmentation nucleus* (Fig. 311, D). This body has the conventional nuclear structure—namely, an achromatic network with the chromatic reticulum mingled with it—and the whole is covered by a nuclear membrane. The chromatic substance, it will be perceived, is now restored to the original amount present in either germ-cell before its maturation, one-half of

[1] W. Pfeffer: *Untersuchungen aus dem Botanischen Institut zu Tübingen*, i., 1884.

it having come, how-
ever, from the male cell
and one-half from the
female cell. On the
commonly a c c e p t e d
theory that this is the
hereditary   substance,
the first segmentation
nucleus contains within
itself potentially all the
inherited qualities of
the future individual.

While the head of
the   spermatozoon   is
making its way through
the substance of the egg
there appears beside it
a minute cytoplasmic
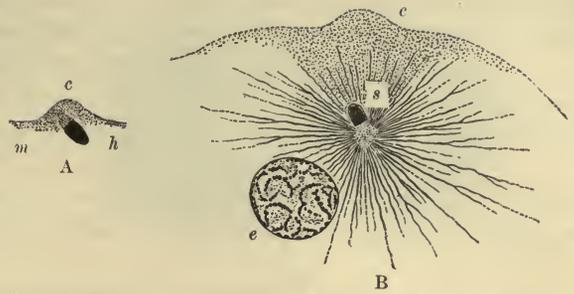
Fig. 310.—Stages in the fertilization of the egg (after Wilson). The drawings were made from sections of the eggs of the sea-urchin, *Toxopneustes variegatus*, Ag.

A. The surface of the egg has become elevated to form *c*, the entrance-cone for the spermatozoon; the head (*h*) and the middle-piece (*m*) of the latter have entered the egg.

B. Five minutes after entrance of the spermatozoon. The head (*s*), now the male pronucleus, has rotated 180 degrees, and has travelled deeper into the ovum. The cytoplasm of the latter has become arranged in a radiate manner about the middle-piece of the spermatozoon, now the centrosome, to form the sperm-aster; *e*, the egg-nucleus, now the female pronucleus, is approaching the sperm-nucleus; its chromatin forms an irregular reticulum; *c*, the entrance cone.
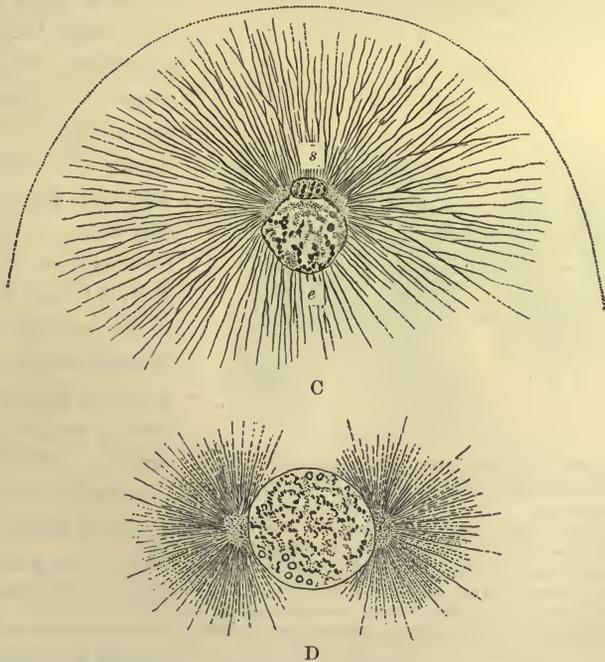
Fig. 311.—Stages in the fertilization of the egg (continued from Fig. 310).

C. Ten minutes after entrance of the spermatozoon. The male and the female pronuclei have met near the centre of the egg and the fusion has begun; the former has become enlarged and its chromatin has become loosely reticulated. The sperm-aster has become enormously enlarged. The single centrosome has been divided into two, which lie upon either side of the sperm-nucleus.

D. The pause thirty minutes after entrance of the spermatozoon. The two pronuclei have fused completely to form the first segmentation-nucleus, all trace of a distinction between paternal and maternal chromatin being lost. The sperm-aster has become divided into two asters, which have moved to opposite poles of the nucleus; the astral rays have become shortened. The egg is now ready to undergo segmentation.

A

B

C
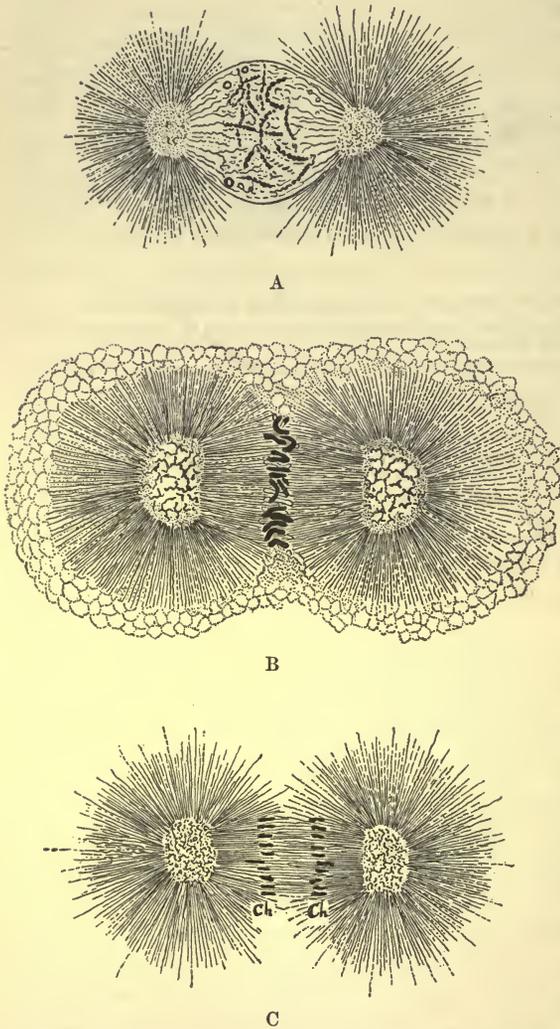
FIG. 312.—Stages in the segmentation of the egg (after Wilson). The drawings were made from sections of eggs of the sea-urchin, *Toxopneustes variegatus*, Ag.

A. Beginning of the formation of the amphiaster. The nuclear membrane has disappeared at the two poles of the spindle-shaped nucleus. Within the nucleus a distinction between the chromatic and the achromatic substance is being made, the former existing as irregular rod-shaped bodies lying at the centre, the latter as delicate filaments extending irregularly from pole to pole. The asters are well marked.

B. The nuclear membrane has wholly disappeared. The chromosomes are clearly defined and aggregated in the centre of the spindle to form the equatorial plate. The achromatic filaments of the spindle are well marked. The connection of the astral rays with the cytoplasmic reticulum of the egg is shown.

C. Each chromosome has become split into two, and the latter, *ch*, are being pulled toward the poles.

body, the *centrosome*, and around the latter the filaments of the cytoplasm of the egg arrange themselves in the form of a star, the whole body being known as the *sperm-aster* (Fig. 310, B). We have previously recognized such a structure in the ovum at the time of maturation, and have found it functional in the formation of the polar bodies; after maturation it disappears. The *sperm-aster* accompanies the sperm-nucleus, becomes gradually enlarged, and finally comes to lie, a large and prominent body, beside the segmentation nucleus. Its origin, or, more exactly, the origin of its centrosome, has been greatly disputed, and, at the present time, is understood in few species of animals. Boveri[1] and Wilson[2] find in the sea-urchins that the centrosome is the middle-piece of the spermatozoon and is exclusively of male origin. Several other investigators have observed in other animals its origin from one germ-cell only, usually the male, and it is a question whether its male origin may not be the common one. The significance of this discovery and the function of the aster will be explained in the following section.

[1] Th. Boveri : *loc. cit.*   [2] E. B. Wilson and A. P. Mathews : *Journal of Morphology*, x., 1895.

There results from fertilization, it is perceived, a single cell complete in all its essential parts. This is the starting-point of the new individual. A pause or resting period usually follows fertilization, and then growth begins.

Segmentation.—The process of growth is a complex process of repeated cell-division, increase in bulk, morphological differentiation, and physiological division of labor.

Cell-division is largely, if not wholly, indirect or karyokinetic. The term *segmentation*, or *cleavage*, of the ovum is conveniently applied to the first few
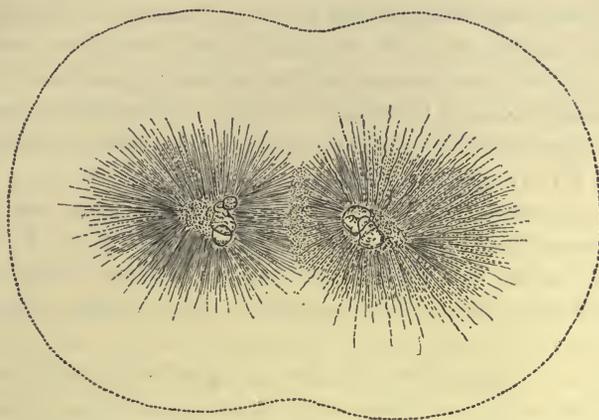
D
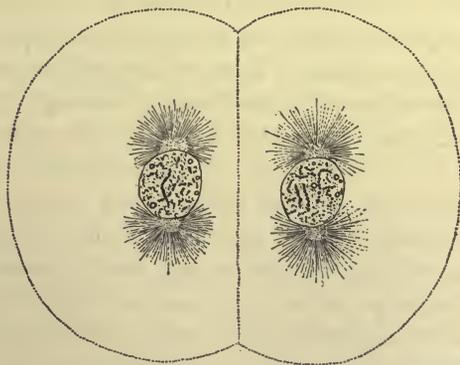
E

FIG. 313.—Stages in the segmentation of the egg (continued from Fig. 312).

D. The divergence of the chromosomes has ceased and the latter have become converted into vesicular masses beside the centrosomes. The spindle is becoming resolved into ordinary cytoplasm. The division of the cytoplasm is beginning with a constriction at the surface of the egg.

E. The vesicular chromatic masses have become converted into two typical resting nuclei, each with a chromatic network. The single aster, formerly connected with each nuclear mass, has become divided into two, which have taken positions at opposite poles of the nuclei. The division of the cytoplasm is complete, and the two resulting cells, or blastomeres, are resting, preparatory to a second division in a plane at right angles to that of the first.

divisions, although the details of segmentation are not different fundamentally from those manifested later in the division of more specialized cells. Each division may be resolved into three definite acts, which, however,

overlap each other in time. The first act is characterized by the appearance of two centrosomes, each with its astral rays, in place of the one already existing (Fig. 311, c). The two take up positions on opposite sides of the nucleus (Fig. 311, D) and await the time when they can exert their specific function. We have spoken of the difference of opinion regarding the origin of the original centrosome of fertilization. The origin of the two centrosomes present in segmentation has likewise been disputed. The question is of considerable theoretical interest in connection with the problem of the physical basis of inheritance. Certain observers have claimed that the centrosomes have a double origin, one being derived from the male and one from the female germ-cell. Upon this theory sexuality is shown by the cytoplasmic centrosomes as well as by the nuclear chromosomes, and the inference is possible that cytoplasm, as well as nucleus, transmits hereditary qualities. The observations of Boveri, Wilson, and others refute this claim by showing that the two centrosomes arise by a splitting of the original centrosome, which is derived from the middle-piece of the spermatozoon. They are, therefore, not male and female, and cannot be regarded as bearers of inherited characteristics. These observations not only allow, but tend to strengthen, the prevailing view of the exclusive hereditary rôle of the nucleus. (See below under Heredity, p. 931).

The second act of segmentation is more complicated than the first, and consists of a halving of the nucleus. The nuclear membrane gradually disappears. The achromatic network resolves itself into long cytoplasmic filaments arranged in the form of a spindle, and meeting at the two centrosomes (Fig. 312, A). The spindle, centrosomes, and asters form the body known as the *amphiaster*. The chromatic substance becomes changed into the definite rod-like *chromosomes* which are collected in the equatorial zone of the spindle and constitute the *equatorial plate* (Fig. 312, B). From the observations of Van Beneden, Rückert,[1] Zoja,[2] and others, it seems probable that the male and the female chromosomes do not fuse together, but remain distinct from each other, perhaps throughout all the tissue-cells. Each chromosome proceeds to split lengthwise, and the two halves are drawn toward the two centrosomes, being mechanically pulled, it is commonly believed, by contraction of the spindle-filaments, assisted by the astral rays (Fig. 312, c). The two halves of the amphiaster, each with its centrosome, are, in fact, commonly believed to be composed of contractile cytoplasm and to be organs possessing the definite function of separating the two halves of the nucleus in karyokinesis. The evidence for this view is not wholly satisfactory. In the process of division each nuclear half obtains half of the original male and half of the original female chromatin, and hence contains inherited potentialities of both parents. After division each half gradually assumes the structure of a typical resting nucleus with its accompanying aster.

The third act of segmentation consists of a simple division of the cytoplasm

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[1] J. Rückert: *Archiv für mikroskopische Anatomie*, xlv., 1895.
[2] R. Zoja: *Anatomischer Anzeiger*, xi., 1896.

into two equal parts, the separation taking place along the plane of nuclear division (Fig. 313, D, E). Each part contains one of the new nuclei, and the result of the first division is the existence of two cells, two blastomeres, in place of the one fertilized ovum. The beginning of differentiation is shown sometimes even as early as this, for, according to Van Beneden, in some mammals at least, one blastomere is often somewhat larger and less granular than the other.

Each blastomere proceeds now to divide by a similar karyokinetic process into two, the result being four in all, and by subsequent divisions, eight, sixteen, and more, the divisions not proceeding, however, with mathematical regularity. By such repeated karyokinetic processes the original fertilized ovum becomes a mass of small and approximately similar cells, the *morula*, from which by continued increase of cells, morphological differentiation, and physiological division of labor, the embryo with all its functions is destined to be built up.

Polyspermy.—It happens occasionally that two or more spermatozoa enter the ovum ; such a phenomenon is known as *dispermy* or *polyspermy*, according to the number of entering sperms. Each sperm with its nucleus and centrosome becomes a male pronucleus and proceeds to conjugate with the female pronucleus. In the case of dispermy the one female and the two male pronuclei fuse together ; each centrosome divides as usual into two, making four in all, which take up a quadrilateral position about the first segmentation nucleus ; the chromatic figure consists of two crossed spindles ; and the egg segments at once into four instead of two blastomeres. When three spermatozoa enter, six centrosomes appear and six blastomeres result from the first division, and analogous phenomena result from more complex cases of polyspermy. Apparently normal larval forms are produced from such double- or multi-fertilized eggs, but as a rule their development ceases very early and death occurs.

During cleavage the ovum proceeds, after the manner of the non-fertilized ovum, slowly along the Fallopian tube and enters the uterus. Unlike the non-fertilized ovum, however, the morula is not cast out of the body, but remains and undergoes further development. The morphological development of the embryo *in utero* does not fall within the scope of the present article. Some attention may, however, be given to the immediate environment of the developing child and its relations to the maternal organism.

Decidua Graviditatis.—While the segmentation of the ovum is proceeding within the Fallopian tube, the uterus prepares for the future guest by beginning to undergo a profound change, probably being stimulated to activity reflexly by centripetal impulses originating in the walls of the tube through contact with the ovum. This change comprises an enlargement of the whole uterus and a great and rapid growth in thickness of its mucosa and its muscular coat. At first the alterations are not unlike the phenomena of growth preceding the menstrual flow, but, as they proceed, they become much more pro-

found than those. The supply of blood to the walls is greatly increased, the vessels forming large irregular sinuses within the mucosa. The supply of lymph is increased. The glands become tortuous and dilated into flattened cavernous spaces, and their walls atrophy, the epithelium breaking down except in their deepest parts. The mucosa is thus converted into a spongy tissue, the framework of which contains numerous large irregular cells, derived probably from the original connective tissue and called *decidual cells*. The musculature is
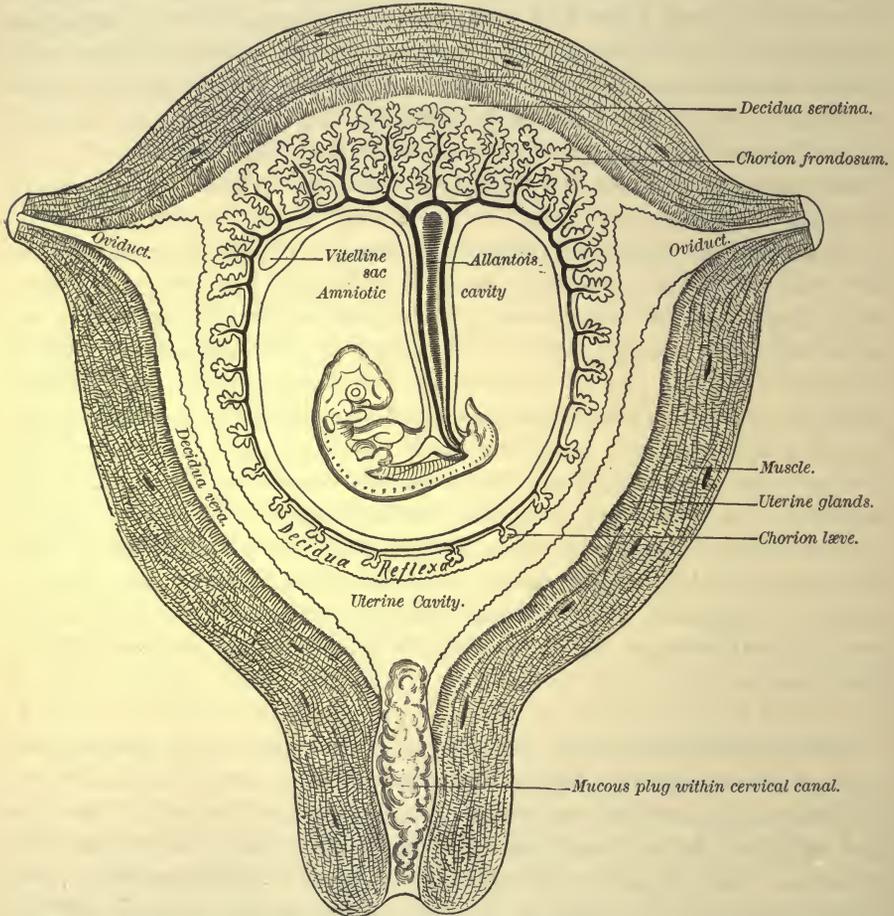
Fig. 314.—Diagram of the human uterus at the seventh or eighth week of pregnancy (modified from Allen Thompson). The fetal villi are shown growing into the sinuses of the decidua serotina and the decidua reflexa; in the latter they are becoming atrophied. They are marked by the black fetal vessels, which can be traced backward along the umbilical cord to the embryo. The placenta comprises the decidua serotina and the chorion frondosum.

greatly thickened by an increase, partly in number and partly in size, of its constituent fibres, and the nerve-supply is increased. These general structural changes proceed through the early part of gestation and are accompanied by special changes to be discussed later. It is not definitely known how far the alterations have gone before the advent of the segmented ovum in the uterus.

With the latter instead of the unimpregnated ovum present in the Fallopian tube, the hypertrophied uterine mucosa does not break away as in menstruation, but remains, and henceforth is called the *decidua graviditatis*, special names being given to special parts. Entering the uterus, the ovum attaches itself in an unknown manner to the wall of the womb. The part of the mucous membrane that forms its bed is henceforth known as the *decidua serotina;* as the seat of the future placenta, it is physiologically the most interesting and important portion of the uterine mucosa. The surrounding cells and tissues are stimulated to active proliferation and grow around and over the ovum, completely covering it with a layer, the *decidua reflexa*. The remainder of the uterine lining membrane constitutes the *decidua vera*. Between the reflexa and the vera is the uterine cavity. At first thickened, the reflexa later thins away as the embryo grows, and approaches close to the vera; finally it touches the latter, and the original cavity of the body of the uterus becomes obliterated. By the sixth month the reflexa disappears, either coalescing with the vera or undergoing total degeneration (Minot). During the latter half of gestation the vera itself thins markedly. This atrophy of the comparatively unimportant reflexa and vera, in contrast to the placental hypertrophy of the serotina, is interesting. The arrangement of the parts is well shown in the accompanying illustration (Fig. 314).

The Fetal Membranes.—The segmented ovum absorbs nutriment at first directly from its surrounding maternal tissues, and later through the mediation of the placenta. Its growth and cell-division are active, and it increases in size and complexity. It early takes the form of a generalized vertebrate embryo, and by the fortieth day begins to assume distinctly human characteristics. It becomes surrounded early by the fetal membranes, which are two in number, the *amnion* and the *chorion* or, as it is usually called in other vertebrates, *false amnion*. The *amnion* is a thin, transparent, non-vascular membrane immediately surrounding the embryo (Fig. 314). In origin a derivative of the embryonic somatopleure, later it becomes completely separated from the body of the embryo. The space enclosed by the amnion, the *amniotic cavity*, within which the embryo lies, is traversed by the umbilical cord and contains a serous fluid, the *liquor amnii*. This fluid, highly variable in quantity, averages at full term nearly a liter (1¾ pints). It has in general the composition of a serous fluid. It contains between 1 and 2 per cent. of solids, consisting of proteids (0.06-0.7 per cent.), mucin, a minute and variable quantity of urea, and inorganic salts. It is derived perhaps in part by exudation from the fetus, but doubtless chiefly by transudation from the maternal fluids, as is indicated by the ready appearance within the amniotic cavity of solutions injected into the maternal veins. It bathes the entire surface of the embryonic body, and is, moreover, apparently swallowed at times into the stomach, as the presence of fetal hairs and epidermal scales within the alimentary canal attests. Its chief functions appear to be those of protecting the fetus from sudden shocks and from pressure, maintaining a constant temperature, and supplying the fetal body with water. The proteid possibly confers upon it a slight nutritive

value, and the minute quantity of urea is perhaps indicative of an unimportant excretory function. As growth proceeds, the amnion expands and becomes loosely attached to the outer fetal membrane, the chorion.

The *chorion* (Fig. 314), or *false amnion*, is formed simultaneously with the true amnion, and like it from somatopleure. It is a thickened vascular membrane, completely surrounding the amnion with the contained embryo. Between it and the amnion there is at first a considerable space, traversed by the umbilical cord and filled with the *chorionic fluid* (which is probably of the same general nature as the amniotic fluid). But later this space is obliterated by the enlargement of the amnion. Externally the chorion presents, at first, a shaggy appearance due to the existence of very numerous columnar processes, called *villi*, extending outward in all directions and joining by their tips the *decidua serotina* and the *decidua reflexa*. Later the villi are aborted except in the region of the serotina, where they become more prominent and constitute an important part of the placenta. The blood-vessels of the chorion are fetal vessels coming from the embryonic structure, the allantois. They comprise the branches and uniting capillaries of the two allantoic or umbilical arteries, and the one (at first two) allantoic or umbilical vein. They are especially well developed within the villi. As growth proceeds, the chorion comes into close contact with the *decidua reflexa*, and, as the latter disappears, with the *decidua vera ;* this portion of it is called *chorion læve*. In the region of the *decidua serotina* it enters into the formation of the placenta, and is here called *chorion frondosum*.

The Placenta.—The *placenta* (Fig. 314), or organ of attachment of mother and fetus, is a disk-shaped body, approximately 20 centimeters (7–8 inches) in diameter, attached to the inner surface of the uterine wall, usually either upon the dorsal or the ventral side, more frequently upon the former, and connected by the umbilical cord with the navel of the fetus. It consists of a maternal part, the modified *decidua serotina*, and a fetal part, the modified chorion, intimately united together. The modifications of the serotina consist of a degeneration of the superficial layers of the mucosa, especially of the epithelium and the glands, and the development of very large irregular sinuses at the surface, into which the uterine arteries and veins appear freely to open. It should be said that it is a disputed question among histologists whether the sinuses are maternal or fetal in origin, or really spaces between maternal and fetal tissues. It is also disputed whether they actually contain blood or only fluid from the surrounding tissues ; the former has by far the weight of evidence in its favor and is the prevailing view. The modifications of the chorion consist of a great increase in length and complexity of branching of the villi, a great development of their contained blood-vessels, and a firm attachment of their tips to the uneven surface of the serotina, so that their branches come to float freely within the uterine sinuses and to be bathed in uterine blood (Fig. 315). The analogy between the mammalian placental villi and the gills of a fish, also highly vascular and floating in liquid, is striking. We shall see later that the analogy is not only morphological, but also physiological,

inasmuch as the villi have important respiratory functions. The bulk of the placenta is this intravillous portion, of spongy consistence, comprising the maternal sinuses permeated by the fetal villi; this is in contact upon the fetal side with the thin unmodified chorion covered within by the amnion, and upon the maternal side with the thin relatively unmodified serotina covered without by the uterine muscle. The pure maternal blood brought by the uterine arteries moves slowly through the sinuses and retires by the uterine veins; the fetal blood is propelled by the fetal heart along the umbilical cord within the allantoic arteries and through the villous capillaries, and returns by the allantoic vein. The two kinds of blood never mix, but are always separated by the thin capillary walls and their thin villous investment of connective tissue and epithelium. Thus the anatomical conditions for ready diffusion are present, and this is the chief means of transfer of nutriment and oxygen from mother to child, and of wastes from child to mother. The physiological rôle of the placenta is, therefore, an all-important and complicated one. The placenta is, technically, the nutritive organ of the embryo.
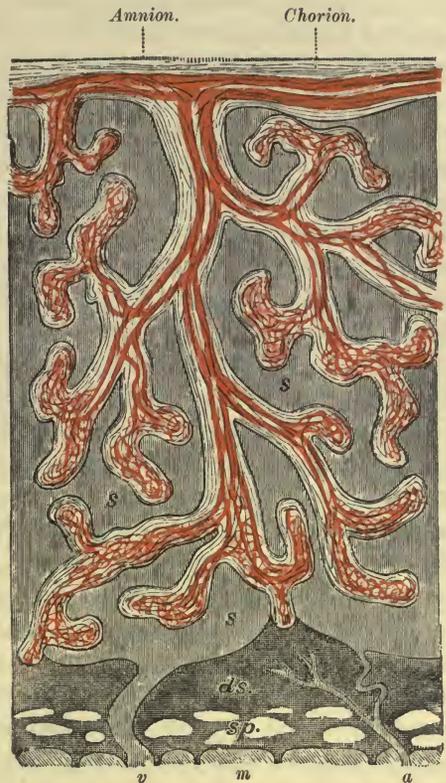
FIG. 315.—Diagram of the placenta (Schäfer): *s*, placental sinuses, into which project the fetal villi, containing the red fetal vessels; *d. s*, decidua serotina; *s. p*, spongy layer, and *m*, muscular layer, of the uterus; *a*, uterine artery, and *v*, uterine vein, opening into the placental sinuses.

Nutrition of the Embryo.—We have seen that a fundamental and most striking difference between the minute human ovum and the large egg of the fowl lies in the relative quantity of food contained in the two. The fowl has retained the primitive habit of discharging the ovum from the maternal body, and discharges within its shell at the same time sufficient food for the needs of the developing chick. Evolution has endowed the human mother, in common with other mammals, with the peculiar custom of retaining the offspring within her body until its embryonic life is completed, and of doling out its nutriment molecularly throughout the period of gestation. The store of nutritive deutoplasm with which the egg leaves the ovary is, therefore, only sufficient for the early segmentative activities. Within the Fallopian tube absorption from the surrounding walls doubtless goes on. Arrived in the uterus and imbedded in

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its decidual wall, the segmented ovum continues to take nutriment from its immediate environing cells. It has been suggested, but without much basis of fact, that the uterine glands, which at this time are greatly dilated, may furnish a nutritive secretion for the use of the embryo; but, *a priori*, it would seem more reasonable that, just as the ovum within the Graafian follicle obtains its food from its surrounding stroma, so within the highly vascular decidua it absorbs directly from the decidual tissue. But that this source soon proves insufficient for the rapid growth is indicated by the early development of the chorion with its villi and the embryonic vascular system. In Reichert's ovum, the earliest known human embryo, and believed to be between twelve and thirteen days old, the villi are already well marked over an equatorial zone. From this time onward throughout gestation the chorion takes an important part in the embryonic nutrition, becoming, as we have seen, an integral part of the placenta. The placenta is *par excellence* the medium of nutritive communication between mother and child.

Let us consider briefly the needs of the embryo. The fetal energies must be directed almost wholly to the all-important functions of growth and preparation for the future independent existence. The organism requires, therefore, an abundance of food containing all the chief kinds of food-stuffs. With the alimentary canal in its embryonic and functionless state, this food, when it reaches the embryo, must necessarily be already digested and ready for absorption by the cells. A supply of oxygen, not necessarily great in quantity, is also needed. The fetal lungs are not ready for respiration, and the oxygen must come to the blood by another channel than them. Carbonic acid must be got rid of, and through other than pulmonary paths. Urea and its forerunners and other wastes, probably not in great quantity, must be excreted. The fetal kidneys and the skin are probably never very active, as is made reasonably certain by the late external opening of the male urethra, the late development of the cutaneous glands, and the composition of the amniotic fluid, into which they would naturally pour their secretions. Thus the paths of income and outgo that are normal to the individual after birth are only partially open during fetal life; nevertheless, the processes of income and outgo must be performed. The placenta, with its close relationship but non-communication of maternal and fetal blood-vessels, has, therefore, been evolved phylogenetically, and appears early in the course of ontogeny. To it is brought on the part of the embryo and discharged into the villous capillaries a mixed blood, comprising venous blood from the various capillary systems of the body, and containing, therefore, the carbonic acid and other wastes of venous blood, and a certain proportion of purified blood that has passed directly by way of the *ductus venosus*, inferior vena cava, right auricle, *foramen ovale*, and the left side of the heart to the aorta and the umbilical arteries. To it is brought on the part of the mother and discharged into the sinuses pure arterial blood, laden with food and with oxygen. Through the membrane intervening between maternal and fetal vessels there passes from the fetus carbonic acid and other wastes, and from the mother food and oxy-

gen. Back to the fetal liver and heart goes the nutritive and arterialized blood, and back to the maternal excretory organs the vessels convey the fetal wastes. The placenta is thus a peculiar organ intermediate between the living cells of the embryo on the one hand and the digestive organs, lungs, kidneys, and skin, of the mother on the other. Little is known of the actual details of the placental process. The structure of the intervening cells indicates that the interchange may be after a manner analogous to that taking place in the lungs, rather than to that of a typical secreting gland—*i. e.* that known physical processes, such as diffusion and filtration, play a prominent rôle. It has been shown by several investigators that the fetus may be poisoned by carbonic oxide and strychnine, and may receive other harmless diffusible substances that are introduced in solution into the maternal circulation. The mother may be affected similarly from the fetal circulation. But, as in the case of the lungs, so the placental membrane can scarcely be regarded as acting in the same passive way as a lifeless membrane would act (compare Respiration. As accessory to the main nutritive source it has been suggested that a diapedesis of maternal leucocytes into the fetus may take place. The uterine glands are thought by some to afford a nutritive secretion to the sinuses, and to the amniotic fluid has been ascribed a nutritive function. Theoretically, these various means are not impossible, but true placental diffusion must be regarded as the chief principle at work. The result is that the mother relieves the child of all the labor of nutrition except that connected directly with the latter's own cellular and protoplasmic metabolism. The fetal energies are, therefore, free to be expended in the process of growth, while gestation profoundly affects the maternal organism.

Physiological Effects of Pregnancy upon the Mother.—As might have been expected, there is probably not one organic system within the mother's body that is not more or less altered by pregnancy, often morphologically, but especially in regard to function. And such normal alterations pass so gradually and so frequently into genuine pathological conditions that it is sometimes difficult to draw the line between the two. The most marked changes are connected with the body of the uterus, and have already been described. The walls of the *cervix uteri* become hypertrophied, though to a less degree than the body, and their glands secrete a quantity of mucus that forms a plug completely closing the passage-way of the cervix (Fig. 314). The rest of the reproductive organs from the uterus outward become involved in the increased venous hyperæmia. The walls of the vagina become infiltrated with serous fluid. The parts of the vulva partake in the general tumefaction. From the second month of gestation onward the mammary glands undergo gradual development as a preparation for the *post-partum* lactation. The increase in size of the laden uterus brings gradually increasing pressure to bear upon the abdominal viscera, and thus mechanically causes functional derangements of the digestive and the urinary organs. The stretching of the abdominal skin results in localized ruptures of the connective tissue of the cutis, the characteristic scars forming the *striæ gravidarum*, which persist after pregnancy.

Other organic changes are, however, more profound than these mechanical ones. In accordance with the increased nutritive labor thrown upon the mother, the total quantity of blood in her body is increased, if we can reason from determinations made upon the lower animals.[1] The condition of the blood is disputed. The old view was that the blood of pregnancy is more watery and contains less hæmoglobin than at other times. This is perhaps true for the earlier months, but Schroeder[2] and others have shown that the proportion of hæmoglobin and the number of red corpuscles rise above the normal during the later stages. The work of the maternal heart is increased during gestation. It is maintained by some that the heart beats more rapidly—according to Kehrer,[3] over eighty in the minute. It has also been thought, mainly from the results of percussion and from sphygmographic tracings, that the left ventricle is hypertrophied during pregnancy. Post-mortem examination, although scanty, cannot be said to confirm this inference. Pregnancy necessarily throws increased labor upon both the liver and the kidneys, and these organs are prone to functional disorders. Gastric disturbances are marked by frequent vomiting. A tendency to increased pigmentation in the skin is present. The nervous system is affected, manifesting its alterations both by nutritional disturbances and by mental irritability, depression of spirits, disordered senses, easily passing into temporary pathological states, and occasionally by feelings of heightened well-being. The body-weight usually increases independently of the added weight of the embryo.

Duration of Gestation.—For centuries the duration of gestation in woman has been commonly regarded as 280 days. The beginning of pregnancy, the union of the ovum and the spermatozoon, however, presents no obvious signs by which it may be recognized, and hence the actual length of pregnancy in the human female is no more known than in other mammals. The obstetrician is obliged, therefore, to use artificial schemes in computing its probable length. Several tables have been published of the time elapsing between a single coition resulting in pregnancy and the terminal parturition. Veit,[4] in collecting 503 such cases reported by several obstetricians, finds the duration to be from 265 to 280 days in 396 cases, and longer in the remaining 107 cases, the variation thus being marked. It is obvious that the date of the effective coition can rarely be known. One of the first and most evident signs of pregnancy is the non-appearance of the menses, and, probably largely from the long-prevailing idea of the close relation existing between ovulation and menstruation, it has been customary to regard gestation as dating from the last menstruation. Following Naegele, obstetricians estimate the date of parturition as 280 days from the first day of the last menstruation; and this simple but artificial rule is doubtless approximately correct.

In accordance with modern biological theories, it must be supposed that for

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[1] O. Spiegelberg und R. Gscheidelen: *Archiv für Gynäkologie*, iv., 1872.

[2] R. Schroeder: *Archiv für Gynäkologie*, xxxix., 1890–91.

[3] F. A. Kehrer: *Ueber die Veränderungen der Pulscurve im Puerperium*, 1886.

[4] J. Veit: *Müller's Handbuch der Geburtshülfe*, 1, 1888.

each species there has been developed a gestative period of a length most favorable to the continuance of the species; this has been a matter of natural selection. But this principle does not account for the termination of the period in any individual case. The proximate cause of the oncoming of birth must be sought in more specific anatomical or physiological phenomena. This cause has been sought long, and not wholly successfully. Among the agents suggested may be mentioned the pressure which the uterine tissues, the cervical ganglion, and the adjacent nerves, receive between the fetal head and the pelvic wall, the stretching of the uterine wall, the fatty degeneration of the deciduæ, the thrombosis of the placental vessels, the venosity of the fetal blood due to the growing functional importance of the fetal right ventricle acting as a stimulus to the placental area, and a gradual increase in irritability of the uterus as the nerve-supply of the organ increases. Some of these, such as the fatty degeneration of the deciduæ and the placental thrombosis, are not constant phenomena, and the others are not definitely proved to be efficient causes. It is probable that, with the uterus undoubtedly irritable, in different cases different stimuli act to inaugurate the process of birth, and *a priori* the above causes seem not improbable ones.

Parturition in General.—Parturition, birth, or labor, is the process of expulsion of the developed embryo, the membranes, and the placenta from the body of the mother. It is executed by contraction of the muscles of the so-called *upper segment* of the uterus and those of the abdominal walls. The *lower segment* of the uterus, comprising approximately that portion of the body lying below the attachment of the peritoneum, the cervix, the vagina, and the vulva, are largely, if not wholly, passive in parturition. The obstetricians have found it convenient to divide labor into three stages, although physiologically these are not sharply differentiated from each other. The first stage is characterized by the dilatation of the *os uteri*, the second by the expulsion of the fetus, the third by the expulsion of the after-birth. The customary position of the fetus within the uterus at the end of pregnancy is that in which the head is downward or nearest the *os*, the back toward the ventral and left side of the mother, and the arms and legs folded upon the trunk.

First Stage of Labor.—For several weeks toward the close of pregnancy there are occasional periods when rhythmic muscular contractions pass over the uterine walls. These are mostly painless, and apparently are not in themselves of special functional importance. The first stage of labor is ushered in by various phenomena, prominent among which are an increase in the intensity of the contractions, their painfulness, and their frequency and continuance. In women they are confined practically to the upper segment of the uterus and its attached ligaments, ceasing at a circular ridge that projects inward and is called the "contraction ring." For some reason, at present disputed, the lower segment of the uterus, and the cervix, are passive. The contractions are probably peristaltic in character, as in lower animals. Schatz[1] has graphically recorded the uterine movements by means of a bladder filled with water

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[1] F. Schatz: *Archiv für Gynäkologie*, xxvii., 1885–86.

and introduced into the uterus. During the earlier part of parturition the contractions gradually increase in intensity up to a maximum which they then maintain. Their rhythm is somewhat irregular; the duration of each contraction averages about one minute, and a pause, which ensues between successive contractions, extends from one and one-half to several minutes. The relaxation of the muscle-fibres during the period of rest is incomplete, the result being that the fibres enter gradually into a tonically contracted state. Each contraction is accompanied by a pain, localized in the early part of labor in the uterus alone, but later extending outward, upward into the abdomen, and downward into the thighs. The pains of labor vary greatly in intensity in individuals, but are usually more intense during the first gestation than during later ones. They are due chiefly to direct mechanical stimulation of the sensory uterine and other nerves by compression, tension, and even laceration.

As a result of the tonic contraction of the uterine walls, gradually increasing with each new peristaltic wave, the uterus becomes gradually narrower in diameter and longer, and the walls press more and more firmly upon the bag of amniotic fluid containing the embryo. Schatz finds that the uterine pressure under the uterine contractions rarely reaches and never exceeds 100 millimeters of mercury. The direction of least resistance to this pressure lies along the cervical canal, the walls of which do not take part in the uterine labor. With each succeeding contraction this canal is forced wider open and the uterine contents are pressed tightly downward and into the cervix. The head of the embryo is preceded by a bulging portion of the membrane, filled with fluid and forming a distinct bladder-like advance guard. This bag appears at the *os uteri*, its contents increase under the increasing pressure, and in the majority of cases, when the os is fully expanded, it bursts and allows the amniotic fluid to escape to the exterior. In some cases the rupture is delayed until the second stage of labor, and rarely the child is born with the membranes intact.

Second Stage of Labor.—The uterine contractions frequently cease for a period following the rupture of the membrane. They then begin anew with increased force, and are accompanied by a new feature, namely, analogous vigorous rhythmic contractions of the muscles of the abdominal walls. These, following deep inspiration and accompanied by forced attempts at expiration with a closed glottis, diminish the longitudinal and the lateral diameters of the abdominal cavity, compress the abdominal organs, and help to augment greatly the uterine pressure. At the beginning of the second stage the force of the contractions is expended mainly upon the head of the embryo, which lies like a plug in the cervical canal. This is squeezed gradually through the os into the vagina, followed by the more easily passing trunk and limbs. The contractions are frequent, vigorous, and painful, the pains reaching a maximum as the sensitive vulva is put upon the stretch and traversed. The vertex is usually presented first to the exterior, the head and body following as the successive contractions of the maternal muscles develop sufficient power to overcome the resistance offered to their passage by the surrounding walls. In

the human female the vaginal muscles do not appear to engage in the expelling act, the uterine and the abdominal muscles alone sufficing and finally forcing the child wholly outside the mother's body. In this gradual manner, painful and dangerous alike to mother and child, the maternal organism forces the offspring to forsake its sheltering and nutritive walls and begin its independent existence.

Third Stage of Labor.—During the later expulsive contractions of the second stage the placenta, being greatly folded by the diminution in the uterine surface of attachment, is loosened from the uterine wall by a rupture taking place through the loose tissue in the region of the blood-sinuses. The child, when born, is joined to the loosened placenta by the umbilical cord, until the latter is tied and cut by the obstetrician. The muscular contractions, now almost painless, continue through the third stage, and the placenta is torn from its attachment, everted, and carried gradually outward. The lining membrane of the uterus from the placenta outward and for a considerable depth is gradually torn free from the deeper parts through the spongy layer, and with the attached chorion and amnion follows the placenta. As a rule, this after-birth appears at the vulva within fifteen minutes after the expulsion of the child; it consists of the placenta, the amnion, the chorion, the *decidua reflexa*, and a considerable portion of the *decidua vera*.

Previous to the third stage slight bleeding from laceration of the passages occurs. But with the loosening of the placenta and the accompanying rupture of the placental vessels the maternal blood flows freely and continues to flow from the uterine wall, chiefly from the placental area, until the after-birth is discharged. The average loss of blood amounts to about 400 grams. At the close of the third stage of labor the uterine contractions have so far proceeded that the organ is compressed into a hard compact mass, the ruptured vessels are contorted and compressed, and the bleeding is thereby largely stopped. For several hours, however, slight hemorrhage continues as an accompaniment to the *post-partum* contractions, but finally this ceases with the formation of a blood-clot over the wounded surface.

The third stage of labor may continue through one or two hours. It is customary, however, for the obstetrician speedily to put an end to it by assisting the removal of the after-birth.

Nature of Labor.—Our knowledge of the nature of the muscular phenomena of labor is incomplete. The uterine contractions are in part automatic and in part reflex, but to what extent the former, and to what the latter, is not known. Nerves reach the uterus partly through the abdominal sympathetic chain and partly directly from the spinal cord through the sacral plexus. Rein[1] found that in the rabbit after section of all uterine nerves normal conception, pregnancy, and birth may occur. In some animals uterine movements may continue after removal of the organ from the body. Such and other observations indicate the existence of an automatic contractile power resident in the organ itself. Since nerve-cells are not found in its walls, it

[1] G. Rein : *Pflüger's Archiv für die gesammte Physiologie,* xxiii., 1880.

seems probable that the automatism resides in the muscle tissue. The uterus is, moreover, very sensitive to direct stimulation, even after excision. In animals higher than rabbits a connection with the lumbar spinal cord seems essential to normal labor. Goltz[1] obtained in dogs conception, pregnancy, and delivery after section of the spinal cord at the height of the first lumbar vertebra. In paraplegic women, with conduction in the cord broken in the dorsal region, delivery is possible. A centre for uterine contraction must hence be supposed to exist in the lumbar cord. Centripetal and centrifugal fibres exist in both sympathetic and spinal nerves, and reflex uterine contractions are readily obtained by stimulation of the central ends of the divided nerve-trunks. According to von Basch and Hofmann,[2] in the dog the sympathetic trunks supply the circular muscular coat of the uterine walls and contain vaso-constrictor fibres, while the spinal trunks supply the longitudinal coat and contain vaso-dilator fibres. Stimulation of the uterus itself, the vagina, the vulva, the sciatic and the crural nerves, and various sensory regions, notably the nipples, causes reflex contractions of the uterus. The same result occurs upon stimulation of various portions of the brain, such as the medulla oblongata, the cerebellum, the pons, the corpora quadrigemina, the optic thalamus, the corpus striatum, and even the corpus callosum. In woman psychic influences may call forth or inhibit uterine contractions. How largely the well-known stimulating effects of the blood in asphyxia and of drugs, like ergot, are due to central, and how largely to direct uterine, influence is undecided. The regular co-ordinated course of labor and many experimental facts make it probable that, normally, reflex influences constitute a large part of the process, the centripetal impulses arising within the uterus itself. In fact, it is customary to speak of labor as a complex reflex action. The undoubted automatism of the uterine muscle-fibres must, however, be taken into account, and the act should be regarded as composed of both automatic and reflex elements. We have here to deal with that variety of contractility peculiar to smooth muscle, in which central and peripheral influences work together to bring about the result. It is perhaps not going too far to regard all such actions, like that of the heart, as primarily automatic and called out by direct stimulation, but as modified and controlled by reflex influences. The parturitive contractions of the striated muscles of the abdominal walls are probably more generally reflex in nature, modified, however, by voluntary efforts.

Multiple Conceptions.—According to the records given by different statisticians, the frequency of twin births varies considerably in different countries. In 13,000,000 births in Prussia, G. Veit[3] found the number of twins to be 1.12 per cent., or 1 in 89 births. In the cities of New York and Philadelphia recent reports give the ratio of twins to single births as 1 : 120, or 0.83 per cent.

[1] Fr. Goltz: *Pflüger's Archiv für die gesammte Physiologie*, ix., 1874.

[2] S. von Basch und E. Hofmann: *Medizinische Jahrbücher*, Wien, 1877.

[3] G. Veit: *Monatsschrift für Geburtskunde und Frauenkrankheiten*, vi., 1855.

Observations of discharged Graafian follicles in cases of multiple conceptions show that twins may arise either from separate eggs or from a single egg. The presence at birth of a double chorion is commonly regarded as diagnostic of the former origin, that of a single chorion of the latter. In the former case the two ova may come from a single Graafian follicle, or from two follicles situated within one ovary, or from both ovaries, direct observation of the ovaries themselves being required to determine the origin in any particular case. The two ova are discharged and fertilized probably at approximately the same time. There are two distinct amnions. The two placentas may be either fused into one or wholly separated from each other, and accordingly the *decidua reflexa* may be single or double. The two offspring may be of separate sexes, and do not necessarily closely resemble each other. In cases where the two embryos come from a single ovum their origin is little understood. It is conceivable that it may arise from the presence of two nuclei within the one ovum. It is more probable, however, that it is due to a mechanical separation of the blastomeres after the first cleavage or later in segmentation.[1] Driesch,[2] Wilson,[3] Zoja,[4] and others have shown that in various invertebrates and the low vertebrate *Amphioxus*, single blastomeres, isolated from the rest by shaking or other unusual treatment, are capable of developing into small but otherwise normal and complete embryos. No reason is obvious why such an occurrence cannot take place in human development, if in any accidental manner within the Fallopian tube the blastomeres become separated. Driesch observed in the sea-urchins and Wilson in *Amphioxus* incomplete separation of blastomeres to produce two incomplete organisms more or less united together. It is not improbable that even in man cases like the Siamese Twins, and greater monstrosities, may be similarly accounted for. In cases of double pregnancy from a single ovum the two amnions are usually separate, in rare cases a breaking away of their partition wall throwing them into one; the two placentas usually fuse more or less into one, the blood-vessels of the two halves always anastomosing; and a single *decidua reflexa* covers both. The two offspring are uniformly of the same sex and their personal resemblance is always close.

In Veit's statistics of 13,000,000 births in Prussia, triplets occur with a frequency of 0.012 per cent., or 1 in 7910, and quadruplets 1 in 371,126 births. There are well-authenticated cases of quintuplets. In all of these cases a single ovum rarely, if ever, contributes more than two embryos, and these are characterized, as in the case of twins, by being of similar sex, by possessing a single chorion, and by close personal resemblance.

The Determination of Sex.—In most, if not all, civilized races more boys are born than girls. This is shown in the following table:[5]

[1] *Cf.* Fr. Ahlfeld: *Archiv für Gynäkologie,* ix., 1876.

[2] H. Driesch: *Zeitschrift für wissenschaftliche Zoologie,* liii., 1892; lv., 1893; *Mittheilungen aus der Zoologischen Station zu Neapel,* xi., 1893.

[3] E. B. Wilson: *Journal of Morphology,* viii., 1893.

[4] R. Zoja: *Archiv für Entwickelungsmechanik der Organismen,* ii., 1895.

[5] *Bulletin de l'institut international de statistique,* vii.

Boys born to 1000 Girls born (1887–91).

Italy	1058	England	1036
Ireland	1055	Connecticut	1072
German Empire	1052	Rhode Island	1049
France	1046	Massachusetts	1046

The proportional birth-rate of the two sexes is usually fairly constant from year to year. This means that constant regulating factors are at work. What determines sex in any one individual is ill understood. The sexual organs in the human embryo are well differentiated at the eighth week of intra-uterine life, hence the sex of the child must be settled previously to this time. It is at present quite impossible to say whether it is settled in the germ-cells previous to their union, in the act of fertilization, or during the early uterine life. Many facts, both observational and experimental, and more hypotheses, bearing upon the determination of sex, have been brought forward. The Hofacker-Sadler law (Hofacker, 1828; Sadler, 1830) is well known, as follows: If the father be older than the mother, more boys than girls will be born; if the parents be of equal age, slightly more girls than boys; if the mother be older than the father, the probability of girls is still greater. Since its promulgation this so-called law has received evidence both confirmatory and contradictory of its truth. Thury in 1863 claimed that the earlier after its liberation the egg is fertilized, the greater is the tendency to the production of a female; the later the fertilization, the greater the probability of a male. Breeders have made use of this principle apparently with success—offspring conceived at the beginning of "heat" seem to be more usually females. Likewise, it is frequently believed that in human beings conceptions immediately after menstruation produce a larger proportion of females than later conceptions. Düsing[1] accepts Thury's view and extends it to the male element—the younger the spermatozoon the greater the tendency toward the production of males. Hence among animals the scarcity of one sex leads to the more frequent exercise of its reproductive function, the employment of younger germ-cells, and therefore the relative increase of that sex. Further, the nearer a parent is to the height of his reproductive capacity the less will be the probability of transmitting his own sex to the offspring. By feeding tadpoles with highly nutritious flesh Yung[2] increased the percentage of females from 56 to 92. Mrs. Treat[3] showed that the butterflies of well-fed caterpillars become females, those of starved caterpillars males. Statistics among mammals and human beings indicate that the proportion of male to female offspring varies inversely with the nutrition of the parents, especially of the mother. Thus, more boys are born in the country than in the city, and in poor than in prosperous families; the relative number of boys is said to vary even with the prices of food. It is contended, moreover, and with some statistical support, that in the human race an epidemic or a war, either of which affects adversely the well-being of the people, is followed by a relative increase

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[1] K. Düsing: *Jenaische Zeitschrift für Naturwissenschaft,* xvi., 1883, and xvii., 1884.

[2] E. Yung: *Comptes rendus de l'Académie des sciences,* Paris, xcii., 1881.

[3] Mrs. Mary Treat: *The American Naturalist,* vii., 1873.

of male births. It is claimed that ethnic intermixture causes a decrease in the relative number of males born. This is strongly supported by a recent statistical study by Ripley [1] of the two races inhabiting Belgium, the Walloons, of the same origin as the Kelts in France, and the Flemish, of German stock. Where these races are purest, the number of boys born to 1000 girls is 1064; along the region where the two races come into contact, however, the number may fall as low as 1043. Maupas [2] found that sex in the rotifer, *Hydatina senta*, could be controlled by altering the temperature of the medium surrounding the egg-laying females. In various experiments at a temperature of 26°–28° C., 81–100 per cent. of the eggs gave rise to males, the rest to females; at 14°–15° C. only 5–24 per cent. were males, the much larger majority females.

The above considerations are highly interesting and suggestive, but they have not yet been brought under general laws sufficiently to make their bearing upon the main problem wholly clear. It is probable that numerous factors are of influence in the determination of sex. The general deduction from all the facts seems justified that unfavorable nutritive conditions surrounding the parents tend to the production of males, favorable conditions to the production of females. The experimental results indicate, moreover, that the conditions surrounding the parents or the developing embryo are largely responsible for the resulting sex. Watase [3] regards the embryo as neutral as regards sex from the time of fertilization up to a certain stage of its development; external conditions act as a stimulus to the sexless protoplasm, and the resulting response is a development in the direction of either maleness or femaleness according to the nature of the stimulus. How largely and in what manner this may be true of the human species is wholly unknown. Düsing urges that the various factors determining sex have arisen through natural selection; they are conducive to the continuance of the species, and they act in such a way that sex is in a certain sense self-regulating—the scarcity of one sex tends to the greater production of individuals of that sex; this is instanced by the fact mentioned above that after the destruction of males by war relatively more males are born than previously.

E. Epochs in the Physiological Life of the Individual.

Fertilization begins, somatic death ends, the physiological life of the individual. Between these two events the life-processes go on gradually, and, with the exception of birth, are marked by few abrupt changes. It is sometimes convenient to divide the individual life into a number of successive stages, as follows: the embryonic period, the fetal period, infancy, childhood, youth, or adolescence, maturity, and old age, or senescence. Such a division, however, is not physiologically exact, the stages are not sharply limited, and the terms are employed in very different senses by different writers. Between fertilization and birth the functions originate and are developed gradually.

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[1] W. Z. Ripley: *Quarterly Publications of the American Statistical Association*, v., March, 1896.

[2] E. Maupas: *Comptes rendus de l'Académie des sciences*, Paris, cxiii., 1891.

[3] S. Watase: *Journal of Morphology*, vi., 1892.

At birth the environment of the individual is abruptly changed, organic connection with the mother suddenly ceases, and profound physiological changes occur. At this time, or shortly after it, the individual is capable of performing all the functions of adult life with the exception of reproduction, the functions needing, however, to be exercised and improved before they are at their best. From birth to maturity, therefore, the physiological history is mainly a history of progressive modifications of function—modifications, indeed, of great importance, but secondary to the primary fact of function itself. The same may be said of the period of old age, with the difference that here the modifications of function are retrogressive. In the present book, devoted mainly to the physiology of the adult at the time of maturity, little can be said of the origin and development of function in the embryo; the modifications of function at different periods of life have been discussed in connection with the various functions themselves; certain topics of special physiological significance have, however, been left for brief treatment in this chapter.

Growth of the Cells, the Tissues, and the Organs.—All growth, whether of the cells, the tissues, or the organs, is the result of no more than three processes, viz. multiplication of cells, enlargement of cells, and deposition of intercellular substance, the first two processes being the most potent of all. Increase in the number of cells is largely, although not wholly, an embryonic phenomenon; increase in the size of cells and deposition of intercellular substance are especially important from the later embryonic period through the time of birth and up to the cessation of the body-growth. The periods of growth of the several tissues differ; in view of this it is quite impossible to designate any period except that of death at which the growth of the tissues wholly terminates. Detailed statistics of the growth of organs are wanting.

Growth of the Body before Birth.—The most obvious result of growth of the cells, the tissues, and the organs, is growth or increase in size of the body. Growth of the body continues actively from the beginning of the segmentation of the ovum up to about the age of twenty-five years, and results in an increase in all dimensions and in weight. In determining the extent of growth, the two most convenient and most commonly used measurements are those of length, or height, and weight. For the embryo the following table has been compiled by Hecker:[1]

Table showing the Average Length and Weight of the Human Embryo at Different Ages.

Month.	Length of embryo in centimeters.	Weight of embryo in grams.
Third	4 to 9	11
Fourth	10 to 17	57
Fifth	18 to 27	284
Sixth	28 to 34	634
Seventh	35 to 38	1218
Eighth	39 to 41	1569
Ninth	42 to 44	1971
Tenth	45 to 47	2334

[1] C. Hecker: *Monatsschrift für Geburtskunde und Frauenkrankheiten*, xxvii., 1866.

The length and the weight at birth vary very greatly. The average measurements, as given for over 450 infants in Great Britain, are, for height, males 19.5 inches, females 19.3 inches; for weight, males 7.1 pounds, females, 6.9 pounds. The weight at birth is said to be greater the nearer the mother's age is to thirty-five years, the greater the weight of the mother, the greater the number of previous pregnancies, and the earlier the appearance of the first menstruation. Race and climate are also of influence. Minot[1] believes that all of these influences work principally through prolonging or abbreviating the period of gestation, and that the variations at birth depend partly upon the duration of gestation and partly upon individual differences of the rate of growth in the uterus.

Growth of the Body after Birth.—In studying the growth of the body after birth two methods have been employed, named the "generalizing" and
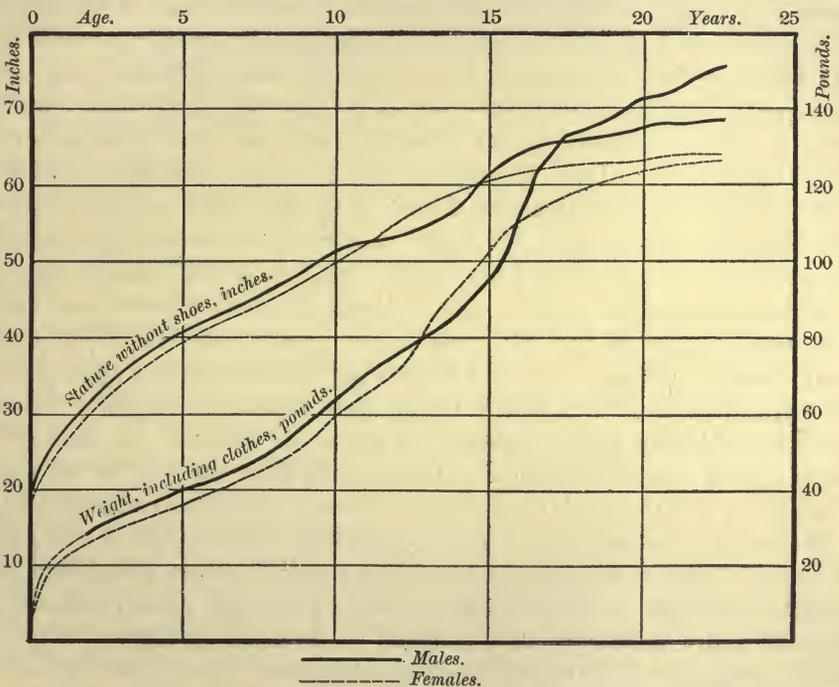
Fig. 316.—Diagram showing increase of stature and weight of both sexes, as determined by the Anthropometric Committee of the British Association.[2]

the "individualizing" methods. The former consists in deducing the course of growth by averages or other central values from statistics taken from a large number of individuals at different ages. It is the method more commonly employed; it shows the course of growth of the typical child, but is inexact in enabling future growth to be predicted in individual cases. The individualizing method consists in measuring the actual growth of the same individual through successive years; it shows well the relation of the indi-

[1] C. S. Minot: *Human Embryology,* 1892.
[2] Roberts: *Manual of Anthropometry,* 1878.

vidual to the type throughout the period of growth. The course of growth of British boys and girls from birth up to the age of twenty-four is graphically shown in the accompanying diagram (Fig. 316). Growth is here seen to be rapid during the first five years of life, then slower up to the tenth or the twelfth year. From thence up to the fifteenth or the seventeenth year —that is, preceding and including puberty—marked acceleration occurs, which in turn is followed by slow increase up to the twentieth or the twenty-fifth year. For from five to ten years thereafter slight increase in height occurs, while from the accumulation of fat the weight usually rises markedly up to the fiftieth or the sixtieth year. One of the most interesting results revealed by statistics is the relative growth of the two sexes. From birth up to about the age of ten or twelve, boys show a slight and increasing preponderance over girls, but the two curves are nearly parallel. The prepubertal acceleration of growth in girls, however, precedes that of boys, and is even accompanied by some check in the male growth, with the result that between the ages of twelve and fifteen girls are actually heavier and taller than boys. This fact, first pointed out in 1872 by Bowditch [1] from observations on several thousand Boston school children, has been abundantly confirmed by Pagliani in Italy, Key in Sweden, Schmidt in Germany, Porter in St. Louis, and others. At about fifteen years boys again take the lead and maintain it throughout life. Boys grow most rapidly at sixteen, girls at thirteen or fourteen, years of age; the former attain their adult stature approximately at twenty-three to twenty-five, the latter at twenty to twenty-one years. The details of growth and the actual measurements vary considerably with race; thus the supremacy of the American girl over her brother appears to be less marked and to cover a shorter period than that of the English, German, Swedish, or Italian girl. Children of well-to-do families are superior to others in both weight and stature. Disease may alter the form of the curve of growth. But the final result seems to depend less upon external conditions than upon race and sex. As an interesting accessory fact it was found by Porter [2] that well-developed children take a higher rank in school than less-developed children of the same age. If the percentage annual increase of the total weight be computed, it is found to diminish throughout life, very rapidly during the first two or three years, later more slowly and with minor variations of increase and decrease; that is, as growth proceeds and the powers of the individual mature, the power to grow becomes rapidly less. This is a peculiar and most interesting fact and has not been explained. It would seem to signify that the sum of the vital powers declines from birth onward. Many facts indicate that the common conception, dating from the time of Aristotle, of human life as consisting of the three periods of rise, maturity, and decline, must give way to a more rational idea of a steady decline from birth.

[1] H. P. Bowditch: *Eighth Annual Report of the State Board of Health of Massachusetts*, 1877.

[2] W. T. Porter: "The Physical Basis of Precocity and Dullness," *Transactions of the Academy of Science of St. Louis*, vi., No. 7, 1893. See also "The Growth of St. Louis Children," *Transactions of the Academy of Science of St. Louis*, vi., No. 12, 1894.

Puberty.—By puberty is meant the period of sexual maturity, at which the individual becomes able to reproduce. In the male the exact time of its onset, characterized primarily by the appearance of fully ripe spermatozoa, is not well known, but is believed to be about one year later than in the female. In temperate climates, therefore, it usually appears in boys not before the age of fifteen; it is earlier in warmer regions. It is preceded and accompanied by acceleration in bodily growth, already spoken of. Other bodily changes, such as general maturation of the functions of the reproductive organs, alterations in the bodily proportions, increase of strength, and growth of the beard, all of which are elements of the transformation from boyhood to manhood, either occur at that time or follow soon after. One of the most obvious external changes is that of the voice. Its tone may fall permanently an octave, and for the time being become rough, broken, and uncontrollable. This is due to a sudden general enlargement of the laryngeal cartilages and a lengthening of the vocal cords.

In the girl the oncoming of puberty is marked more exactly than in the boy by the appearance of menstruation, in the majority of girls in temperate climates at the age of fourteen to seventeen. But other characteristic anatomical and physiological changes in the body occur. The uterus, the external reproductive organs, and the breasts become larger, while the pelvis widens. The prepubertal acceleration of growth has been mentioned. Nervous disorders are especially prone to make their appearance at this time. The subcutaneous layer of adipose tissue develops and confers upon the outlines the graceful curves characteristic of the woman's body. The mental faculties mature, and the girl becomes a woman earlier and more rapidly than the boy a man.

Climacteric.—From the sixtieth year the power of producing spermatozoa, and, therefore, the reproductive power of man, begins to wane. It continues, however, in a diminishing degree, even to extreme old age, and there is no recognized period of ending of the male sexual life.

In woman, on the other hand, the sexual period continues for only thirty to thirty-five years, and the climacteric, menopause, or change of life, marks a definite ending of the power of reproduction. In temperate climates it occurs usually between the ages of forty-four and forty-seven; in warmer regions it comes early, in colder late. It is earlier in the laboring classes, and later where menstruation has first appeared early. Its most characteristic feature is the cessation of menstruation, which is a gradual process extending over a period of two or three years and characterized by irregularity in the oncoming and the quantity of the flow and by gradual diminution. But the cessation of the menses is but one phenomenon in a long series of changes that profoundly affect the whole organism and endanger life. The reproductive organs and the breasts diminish in size, and ovulation ceases. The changes in the pelvic organs are in general the reverse of those occurring at puberty. The organic functions generally are rendered irregular; dyspepsia, palpitation, sweating, and vasomotor changes are frequent; vertigo, neuralgia, rheumatism, and gout are not rare; a tendency to obesity occurs, though sometimes the reverse; irritability, fear, hysteria, and melancholia may be present; the

disposition may be temporarily altered,—all of which changes indicate that the female organism at this time suffers a profound nervous shock. The loss of the weighty function of reproduction and the adaptation to the new order of events is not accomplished quietly.

Senescence.—The progressive diminution in the power of growth from birth onward throughout life has been mentioned, and may be interpreted as indicating that the process of senescence begins with the beginning of life.[1] In the broadest sense this is true, and is confirmed by a study of various organic functions. In the more restricted sense senescence or old age comprises the period from about fifty years (in woman from the climacteric) onward, during which there is a noticeable progressive waning of the vital powers. The leading somatic changes accompanying old age are atrophic and degenerative, but detailed statistics of this period are almost wholly wanting. A marked cellular difference between the young and the old, which is shown by nearly if not quite all tissues, is the relatively large nucleus and small quantity of cytoplasm in the young, the proportions being reversed in the old. This has recently been pointed out as follows by Hodge[2] in the nerve-cells of the first cervical spinal ganglion :

	Volume of nucleus.	Nucleoli observable in nuclei.	Pigment much.	Pigment little.
Fetus (at birth)	100 per cent.	in 53 per cent.		
Old man (at ninety-two years)	64.2 "	in 5 "	67 per cent.	33 per cent.

Thus with the progress of age the nuclei become small and irregular in outline, and the cytoplasm pigmented, while the nucleoli are often wanting. The nuclear differences are even more marked in the cerebral ganglia of bees, where, moreover, aged individuals possess a smaller number of nerve-cells than the young. They are in harmony with the growing belief in the function of the nucleus as the formative centre of the cell. It has been shown that a decrease in the weight of the whole brain occurs in both men and women, beginning in the former at about fifty-five years, in the latter at about forty-five years. In eminent men the decrease begins later. The thickness of the cortex and the number of tangential fibres in it diminish especially after fifty years, and this probably signifies a loss of cells. There is a decrease in general brain-power, in power of origination, in the power to map out new paths of conduction and association in the central nervous system and thus to form habits. Reaction-time is lengthened. The delicacy of the sense-organs is noticeably less, and in the eye the hardening of the crystalline lens and the weakening of the ciliary muscle diminish the power of accommodation. The muscles atrophy and muscular strength is reduced. The pineal gland, ligaments, tendons, cartilage, and the walls of the arteries, show a tendency toward calcification, and the bones become more brittle. Subcutaneous adipose tissue disappears, but a fatty degeneration of cells is not uncommon, notably in all varieties of muscle-cells, in nerve-cells, and probably in gland-cells. The pigment of the hairs disap-

[1] *Cf.* C. S. Minot: *Journal of Physiology*, xii., 1891.
[2] C. F. Hodge: *Anatomischer Anzeiger*, ix., 1894 ; *Journal of Physiology*, xvii., 1894.

pears. The size of the muscles, the liver, the spleen, the lymphatic and probably the digestive glands, decreases. The heart and the kidneys seem to retain their adult size. The vital capacity of the lungs, the amounts of carbonic acid and of urine excreted, diminish. The rate of respiration and of the heart-beat rises slightly. Ovulation is wanting, and the power of producing spermatozoa is lessened. The stature undergoes a slight and steady decrease. Boas[1] has shown that in the North American Indian this continues from about thirty years of age onward. All of these changes, the details of which should be carefully studied and reduced to anatomical and physiological exactness, demonstrate that senescence is characterized by a steady diminution of vitality.

Death.—Sooner or later vitality must cease and the change that is called death must come. The term "death" is used in two senses, according as it is applied to the whole organism or to the individual tissues of which the organism is composed. The former is distinguished as somatic death, or death simply, the latter as the death of the tissues.

Somatic death occurs when one or more of the organic functions is so disturbed that the harmonious exercise of all the functions becomes impossible. Thus, if the brain receives a severe concussion, the co-ordination of the organs may be interrupted ; if the respiration ceases, the necessary oxygen is withheld ; if the heart fails, the distribution of oxygen and food and the collection of wastes come to an end ; if the kidneys are diseased, the poisonous urea is retained within the tissues. A continuation of any one of these profound abnormal conditions, which may be brought about by accident or disease, or a simultaneous occurrence of several slight disturbances of function, such as is not infrequent in aged persons, may prevent the restoration of that concordance among the organs without which the individual cannot live. The most convenient and most certain sign by which somatic death may be recognized is the absence of the beat of the heart, and in nearly all cases this is the criterion employed. But it should be borne in mind that the failure of the heart to beat is but one of the causes, and frequently a very secondary one, the primary cause being then associated with other functions. It is at present in most cases quite impossible to trace the course of events by which the derangement of one function leads to the ultimate cessation of individual life.

Death of the tissues or of the living substance is neither necessarily nor usually simultaneous with somatic death. Constantly throughout life the molecules of living matter are being disintegrated, and whole cells die and are cast away ; life and death are concomitants. With the cessation of the individual life the nervous system dies almost immediately. With the muscular tissue it is very different. The stopping of the beat of the heart is a gradual process, and, as Harvey long ago pointed out, the last portion to beat, the *ultimum moriens*, is the right auricle. For many minutes after death the heart, if exposed, will be found to be excitable and to respond by single contractions to single stimuli. Irritability is said to continue in the smooth muscle of the stomach and the intestines for forty-five minutes, and considerably later than

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[1] F. Boas: *Verhandlungen der Berliner Anthropologischen Gesellschaft*, 1895.

this the striated muscles of the limbs can be made to twitch by proper stimuli. Gland-cells probably die within a few minutes. As to the chemical changes undergone by the protoplasm in the process of dying, little can be said. The composition of dead protoplasm is comparatively well known, that of living protoplasm is at present a blank; and, although investigation has gone sufficiently far to offer a basis for several suggestive hypotheses, the latter are too abstruse for lucid discussion in the present space. Neither in somatic death nor in the death of the tissues does the body lose weight. Within fifteen or twenty hours it cools to the temperature of the surrounding medium. Rigor mortis, due to the coagulation of the muscle-plasma within the muscle-cells, begins within a time varying with the cause of death from a half hour to twenty or thirty hours, and continues upon an average twenty-four to thirty-six hours. Then the tissues soften, and soon putrefactive changes begin.

Theory of Death.—It has been intimated that all the tissues are destined to die. An exception must be made in the case of those germ-cells, both male and female, that are employed in the production of new individuals. They pass from one individual, the parent, to another, the offspring, and thus cannot be said to undergo death. This is the basis of Weismann's theory of the origin and significance of death in the organic world.[1] According to Weismann, primitive protoplasm was not endowed with the property of death. As found in the simplest individuals, like the *Amœba*, even at the present day, with a continuance of the proper nutritive conditions protoplasm does not grow old and die; the single individual divides into two and life continues unceasing, unless accident or other untoward event interferes. With the progress of evolution, however, the cells of the individual body have become differentiated into germ-cells and somatic cells, the former subserving the reproduction of the species, the latter all the other bodily functions. Germ-cells are passed on from parent to offspring; they never die, they are immortal. Somatic cells, on the other hand, grow old, and at last perish. Death was, therefore, in the beginning, not a necessary adjunct to life; it is not inherent in primitive protoplasm, but has been acquired along with the differentiation of protoplasm into germ-plasm and somatoplasm, and the introduction of a sexual method of reproduction. It has been acquired because it is to the advantage of the species to possess it; in the simplest cases it should occur at the close of the reproductive period, and in fact it frequently does occur then. A superabundance of aged individuals, after they have ceased to be reproductive, would be detrimental to the race; it is to the advantage of the species that they be put out of the way. Death of the individual in order that the species may survive has, therefore, become an established principle of nature. The higher animals are better able to protect themselves from destruction than the lower, and, moreover, they are needed to rear the young; hence the duration of life is frequently prolonged beyond the reproductive period.

Weismann's theory has been the cause of much discussion, and the pros and cons have been set forth by eminent biological authorities. In its appli-

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[1] A. Weismann: *Essays upon Heredity*, i., 1889.

cation to the human race it would seem that the factors of social evolution have brought it about that the aged are protected in the struggle for existence for long after their reproductive usefulness. has ceased, and thus the working of a pitiless biological law has become modified.

F. Heredity.

Biologists are accustomed to recognize two factors as responsible for the character and actions of the living organism. These are heredity and the environment. Heredity includes whatever is transmitted, either as actual or as potential characteristics, by parents to offspring. The environment comprises both material and immaterial components, such as food, water, air, or other substances that surround the organism, and the forces of nature, such as light, heat, electricity, and gravity, that act as conditions of existence or as stimuli to action. The same principles apply to the character and actions of every cell of a many-celled organism, but here we must include in the environmental factor the mysterious influences that are exerted upon the cell by the other cells of the body. Of these two factors heredity acts from within, the environment from without the living substance. Among unicellular organisms the individual begins its career when the bit of protoplasm that constitutes its body is separated from the parent bit of protoplasm. Among higher forms, including man, the term individual may be applied to the fertilized ovum ; the union of the ovum and the spermatozoon inaugurates the new being. From the inception to the death of the individual, life consists partly of manifestations of the powers conferred by the germ-cells and partly of reactions to environmental influences. In considering the details of vital action we are apt to overlook these fundamental facts and to evolve narrow and erroneous views as to the causes of vital phenomena. Biologists are seeking with increasing vigor to determine the relative importance of the parts played by these two principles in development and in daily life. It is needless to say that the problem is a difficult one and is still far from solution. In previous chapters of this book attention has been directed more especially to the external than to the hereditary factor. A work upon physiology would be incomplete, however, if it did not include an examination of the latter, especially since at the present time heredity is one of the leading subjects of biological research and discussion. It is proposed, therefore, in this section to present a brief outline of the facts, the principles, and the attempted explanations of the modes of working of heredity. It should be premised that, because of the present incomplete state of our knowledge of the facts, the highly speculative and involved character of most of the theories, and the constant, active shifting of ideas and points of view, such an outline must necessarily be incomplete and in many respects unsatisfactory.

Facts of Inheritance.—It is not proposed in this paragraph to enter into a discussion of the question as to whether a particular vital phenomenon is a fact of inheritance or a reaction to external influences. For our present purposes it is sufficient to record the common facts of resemblance to ancestors,

and to assume that such resemblance, when present, has been inherited. Resemblances are strongest between child and parents, and appear in a diminishing ratio backward along the ancestral line. Galton[1] has computed that, of the total heritage of the child, each of the two parents contributes one-fourth, each of the four grandparents one-sixteenth, and the remaining one-fourth is handed down by more remote ancestors. The correctness of this estimate has been disputed by Weismann. The fact must not be overlooked that, in addition to and back of all the particular individual features that are inherited, a host of racial characteristics are transmitted—the progeny of a given species belongs to that species; the human being is the father of the human child, the child of Caucasian parents is a Caucasian, of negro parents a negro.

Congenital resemblances may be anatomical, physiological, or psychological, and in each of these classes they may be normal or pathological. Anatomical resemblances are the most commonly recognized of all : facial features, stature, color of eyes and of hair, supernumerary digits, excessive hairiness of body, cleft palate, monstrosities, and various defects of the eye, such as those that give rise to hypermetropia, myopia, cataract, color-blindness, and strabismus, are all known examples. Physiological peculiarities that may be transmitted include the tendency to characteristic gestures, locomotion and other muscular movements, longevity or short life, tendency to thinness or obesity, handwriting, voice, hæmatophilia or tendency to profuse hemorrhage from slight wounds, gout, epilepsy, and asthma. Psychological inheritances comprise habits of mind, talent, artistic and moral qualities, tastes, traits of character, temperament, ambition, insanity and other mental diseases, and tendencies to crime and to suicide.

Latent Characters ; Reversion.—Characters that never appear in the parent may yet be transmitted through him from grandparent to child ; such characters are called *latent.* Among the most striking latent characters are those connected with sex. Darwin[2] says : " In every female all the secondary male characters, and in every male all the secondary female characters, apparently exist in a latent state, ready to be evolved under certain conditions." Thus, a girl may inherit female secondary sexual peculiarities of her paternal grandmother that are latent in her father, or a boy may inherit from his maternal grandfather characteristics that never show in his mother. An excellent example of such transmission, taken from the herbivora, is the common one of a bull conveying to his female descendants the good milking qualities of his female ancestors. In the human species hydrocele, necessarily a disease of the male, has been known to be inherited from the maternal grandfather, and hence must have been latent in the mother's organism. That in such cases the character is really potential, though latent in the intermediate ancestor, is rendered probable by such well-known facts as the appearance of female cha-

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[1] Francis Galton : *Natural Inheritance,* 1889, p. 134.

[2] Charles Darwin : *The Variation of Animals and Plants under Domestication,* vol. ii., 2d ed., 1892.

racteristics in castrated males, and of male characteristics in females with diseased ovaries or after the end of the normal sexual life.

Latency may be offered as the explanation of the numerous cases of *atavism,* or *reversion,* by which is meant the appearance in an individual of peculiarities that were formerly known only in the grandparents or more remote ancestors, but not in the parents of the individual. This subject is one of the most important in the whole field of heredity. Almost any character may reappear even after many generations. In the human species stronger likeness to grandparents than to parents is a frequent occurrence. The majority of the frequent anomalies of the dissecting-room are regarded as reversions toward the simian ancestors of the human race. The crossing of two strains develops a strong tendency to reversion, and because of this the principle of atavism must constantly be taken into account by breeders of animals and growers of plants. As an example of reversion after crossing may be mentioned the well-known one, studied by Darwin, of the frequent appearance of marked stripes upon the legs of the mule, the mule being a hybrid from the horse and the ass, both of which are comparatively unstriped but are undoubtedly descended from a striped zebra-like ancestor. Here the capacity of developing stripes is regarded as latent in both the horse and the ass, but as made evident in the mule by the mysterious influence of crossing. Darwin thinks likewise that the customary degraded state of half-castes may be due to reversion to a primitive savage condition which, usually latent in both civilized and savage races, is rendered manifest in the offspring that results from the union of the two. Reversionary characters are often more prominent during youth than during later life—a fact that has been quoted in favor of their explanation on the theory of latency.

Regeneration.—The facts of regeneration of lost parts must also be taken into account in a theory of heredity. Such regeneration may be either physiological or pathological. *Physiological* or *normal regeneration* has reference to the reproduction of parts that takes place during the normal life of the individual, such as the constant growth of the deeper layers of the epidermis to replace the outer layers that are as constantly being shed. *Pathological regeneration* refers to the replacement of parts lost by accident, and presents the more interesting and striking examples. The power of pathological regeneration in man and the higher mammals is limited. A denuded surface may be re-covered with epithelium; the central end of a cut nerve may grow anew to its termination; the parts of a broken bone may reunite; muscle may reappear; connective-tissue, blood-corpuscles, and blood-vessels may develop readily; and in the healing of every wound a regeneration of parts takes place. But in descending the scale of animal life the regenerative power becomes progressively stronger, and in many plants and low animals it is marvellous. Thus, the newt may replace a lost leg, the crab a lost claw, the snail an eyestalk and eye. If an earth-worm be cut in two, one half may regenerate a new half, complete in all respects. A hydra may be chopped into fragments and each fragment may re-grow into a complete hydra. From

a small piece of the leaf of a begonia, planted in moist earth, a new plant with all its parts may arise. It is evident that the existing parts of an organism, if not too specialized, possess the power of restoring parts that are lost; under ordinary circumstances this power is latent. The growth of tumors is perhaps allied in nature to regeneration. A study of regeneration shows that in many cases the process of building anew follows the same course as the original embryonic growth. It is properly a phenomenon of heredity.

The Inheritance of Acquired Characters.—No topic in heredity has been more debated during the past fifteen years than that of the possibility of the transmission to the offspring of characteristics that are acquired by the parents previous to the discharge of the germ-cells, or, in the case of the mammalian female, previous to parturition. Obviously, no one denies this possibility in the unicellular organisms, where reproduction by fission prevails, for there the protoplasm of the body of one parent becomes the substance of two offspring; in the transformation nothing is lost, and hence whatever peculiarities the ancestral protoplasm has acquired are transferred bodily to the descendants. But in multicellular forms, where sexual reproduction exists, the case is very different, for here whatever is transmitted is transmitted through germinal cells, or *germ-plasm*, as the hereditary substance contained in the germ-cells is now commonly called. The problem then resolves itself into that of the relation of the germ-plasm to the protoplasm of the rest of the body, the so-called *somatoplasm;* and the question to be answered is this: Are variations in the parental somatoplasm capable of inducing such changes in the germ-plasm that somatic peculiarities appear in the offspring similar to those possessed by the parent? Weismann classifies all somatic variations according to their origin into three groups—viz. injuries, functional variations, and variations, mainly climatic, that depend upon the environment. The problem of their inheritance is a far-reaching one, and upon its correct solution depend principles that are of much wider application than simply to matters of heredity; for if acquired characters can be inherited, there is revealed to us a most potent factor in the transformation of species, and the whole question of the possibility of use and disuse as factors of evolution is presented. The larger evolutionary problem need not here be considered.

Regarding the problem of the inheritance of acquired characteristics we may say at once that it is not yet solved. To the lay mind this may seem strange, for at first thought it appears self-evident that parents may transmit to their children peculiarities that they themselves have acquired. Affirmative evidence seems all about us, as witness the undoubted cases of inheritance of artistic tastes, of talent, of traits valuable in professional life, which seem to originate in the industry of the parent. But scientific analysis by Weismann and others of popular impressions, popular anecdotes, and hearsay evidence, and accurate original observation have revealed little that cannot as well be explained on other hypotheses. Anatomical and functional peculiarities of the body that are apparently new often reappear in successive generations, but to assume that they are acquired by the somatoplasm and have become congenital, rather than

that they are germinal from the first, is unwarranted. Direct experiments by various investigators are almost as inconclusive. Weismann[1] has removed the tails of white mice for five successive generations, and yet of 901 young every individual was born with a tail normal in length and in other respects. Bos[2] has experimented similarly upon rats for ten generations without observing any diminution of the tails. The practice of circumcision for centuries has resulted in no reduction of the prepuce. The binding of the feet of Chinese girls has not resulted in any congenital malformation of the Chinese foot. Brown-Séquard,[3] and later Obersteiner,[4] have artificially produced epilepsy in guinea-pigs by various operations upon the central nervous system and the peripheral nerves, and the offspring of such parents have been epileptic. At first this would seem to amount to proof of the actual hereditary transmission of mutila-tions, yet in these cases the mutilation itself was not transmitted; the offspring were weak and sickly and exhibited a variety of abnormal nervous and nutri-tional symptoms, among which was a tendency toward epileptiform convulsions, the cause of which is still to be explained. Evidence from palæontology regarding the apparent gradual accumulation of the effects of use and disuse throughout a long-continued animal series seems to require the assumption of such a principle as the inheritance of acquired characters, but even here the principle of natural selection may perhaps be equally explanatory.

The Inheritance of Diseases.—The question of the inheritance of diseases has also been much discussed. The same general principles apply here as in the inheritance of normal characteristics. The fact has been mentioned above that pathological characters, whether anatomical, physiological, or psycholog-ical, are capable of transmission. If, however, a pathological character has been acquired by the parent and is not inherent in his own germ-cells, it is extremely doubtful whether it can be passed on to the child. A diseased parent, on the other hand, may produce offspring that are constitutionally weak or that are even predisposed toward the parental disease, and such off-spring may develop the parent's ailment. In such cases constitutional weakness or predisposition, and not actual disease, is inherited; the disease itself later attacks the weak or predisposed body. Proneness to mildness or severity of, and immunity toward, certain diseases seem to be transmissible. These sub-jects, however, are so little understood, and the real meaning of such terms as predisposition, inherited constitutional weakness, and inherited immunity, is so little known, that it is idle to discuss them here.

Considerable experimental work has been performed recently upon the transmissibility of infectious diseases. Undoubtedly infectious diseases cling to a particular family for generations. The transmitted factor is probably fre-quently, if not usually, simple predisposition. But in an increasing number of cases there appears to be transmission of a specific micro-organism. Such

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[1] A. Weismann: *Essays upon Heredity*, vol. i., 1889, p. 432.

[2] J. R. Bos: *Biologisches Centralblatt*, xi., 1891, p. 734.

[3] E. Brown-Séquard: *Researches on Epilepsy, etc.*, Boston, 1857; also various later papers.

[4] H. Obersteiner: *Medizinische Jahrbücher*, Wien, 1875, p. 179.

transmission is called *germinal* when the micro-organism is conveyed in the ovum or the semen, and *placental* or *intra-uterine* when the micro-organism reaches the fetus after uterine development has begun, and chiefly through the circulation. Of germinal infections syphilis seems undoubtedly capable of transmission within either the ovum or the semen. The possibility of germinal transmission of tuberculosis has been maintained, but is not fully proven. Of intra-uterine infections there have been observed in human beings apparently undoubted cases of typhoid fever, relapsing fever, scarlatina, small-pox, measles, croupous pneumonia, anthrax, and possibly tuberculosis, syphilis, and Asiatic cholera. It is obvious that neither germinal nor placental inheritance, both taking place through the medium of a specific micro-organism, and not through the modification of germ-plasm, is comparable to inheritance in the customary sense.

Theories of Inheritance.—From early historical times theories of inheritance have not been wanting. Physical and metaphysical, materialistic and spiritualistic theories have had their day. Previous to the discovery of the spermatozoon (Hamm, Leeuwenhoek, 1677) all theories were necessarily fantastic, and for nearly two hundred years later they were crude. The theories that are now rife may be said to date from 1864, when Herbert Spencer published his *Principles of Biology*. Since that date they have become numerous. Even the modern theories are highly speculative; none can be regarded as being accepted to the exclusion of all others by a large majority of scientific workers, and the excuse for introducing them into a text-book of physiology is the hope that a brief discussion of them may prove suggestive, stimulating, and productive of investigation.

Germ-plasm.—*Germinal substance, germ-plasm* (Weismann), or, as it is sometimes called, *idioplasm* (Nägeli), must lie at the basis of all scientific theories of heredity. The father and the mother contribute to the child the spermatozoon and the ovum respectively, and within these two bits of protoplasm there must be contained potentially the qualities of the two parents. There is much evidence in favor of the prevailing view that the nucleus alone of each germ-cell is essentially hereditary, or, more exactly, that the chromatic substance of the nucleus is the sole actual germinal substance. We have seen that the tail of the spermatozoon is a locomotive organ, and that the body of the ovum is nutritive matter. We have seen also that the essence of the whole process of fertilization is a fusion of the male and the female nuclei, or, more exactly, a mingling of male and female chromosomes. Hence most physiologists agree with Strasburger and Hertwig that the chromatic substance of the nuclei of the germ-cells transmits the hereditary qualities.

As to the origin of the germ-plasm, two hypotheses have been suggested. Spencer, Darwin, Galton, and Brooks have argued in favor of a production of germ-plasm within each individual by a collocation within the reproductive organs of minute elementary vital particles—"physiological units" (Spencer), "gemmules" (Darwin)—that come from all parts of the body; hence each part of the body has its representative within every germ-cell. This hypothesis

affords a ready explanation of numerous facts, but its highly speculative character, the entire absence of direct observational or experimental proof of its truth, and the demand that its conception makes upon human credulity, militate against its general acceptance. Weismann, the promulgator of the second hypothesis, denies altogether the formation of the germ-plasm from the body-tissues of the individual, and maintains its sole origin from the germ-plasm of the parent of the individual. Through the parent it comes from the grandparent, thence from the great-grandparent, and so may be traced backward through families and tribes and races to its origin in simple unicellular organisms. According to Weismann, therefore, germ-plasm is very ancient and is directly continuous from one individual to another; the parts of an individual body are derivatives of it, but they do not return to it their representatives in the form of minute particles. The general truth of Weismann's conception can hardly be denied.

As to the morphological nature of germ-plasm, two views likewise are held. One school, led by His and Weismann, holds that germ-plasm possesses a complicated architecture; that the fertilized ovum contains within its structure the rudiments or primary constituents of the various cells, tissues, and organs of which the body is destined to be composed; and that growth is a development of these already existing germs and largely independent of surrounding influences. In accordance with this idea, segmentation of the ovum is specifically a qualitative process, one blastomere representing one portion of the future adult, another blastomere another portion, and so on. This theory recalls in a refined form the crude theory of *Preformation* that was advocated during the seventeenth and eighteenth centuries by Haller, Bonnet, and many others, according to which the germ-cell was believed to contain a minute but perfectly formed model of the adult, which needed only to be enlarged and unfolded in growth. The other modern school, in which Oscar Hertwig is prominent, maintains that the fertilized egg is isotropous—that is, that one part is essentially like another part—that the architecture of the egg is relatively simple, and that growth is largely a reaction of the living substance to external influences. The idea of isotropy is based largely upon the experimental results of Pflüger, Chabry, Driesch, Wilson, Boveri, and the brothers Hertwig, who by various methods and in various animals have found that single blastomeres of a segmenting ovum, when separated from the others, will develop into normal but dwarfed larvæ; that is, a portion of the original germ-plasm is capable of giving rise to all parts of the animal. These results are interpreted to signify that segmentation, instead of being qualitative, is quantitative, each blastomere being like all the others. The second theory, like the first, resembles in some degree a theory of the past two centuries, advocated by Wolff and Harvey, and known as the theory of *Epigenesis.* According to this there was no preformation in the germ-cells, but rather a lack of organization which during growth, under guidance of a mysterious power supposed to be resident in the living substance, gave place to differentiation and the appearance of definite parts.

Modern microscopes have revealed no miniature of the adult in the egg, nor has modern physiology found necessary an assumption of extra-physical forces within living matter. With the increase of knowledge the old and crude preformation of Haller and Bonnet and the speculative epigenesis of Wolff and Harvey have given place to the new preformation and epigenesis of the present time, and all modern theories of heredity may be classed in the one or the other category or as intermediate between them. The modern advocates of preformation explain hereditary resemblance by the supposed similarity of all germ-plasm in any one line of descent. The modern advocates of epigenesis, while allowing the necessity of a material basis of germ-plasm, ascribe hereditary resemblance to similarity of environment during development.

Variation.—It is a commonplace in observation that, however close hereditary resemblance may be, it is never absolute; the child is never the exact image of the parent either physically or mentally. Variations from the parental type may be either *acquired* by the offspring subsequent to fertilization or to birth, and hence are to be traced to the action of the environment; or they may be *congenital,* that is, inherent in the germ-plasm. Although it is not always easy in the case of any one variation to determine to which class it belongs, yet the fact remains that the two classes exist; and a complete theory of heredity must recognize and explain congenital variation as fully as congenital resemblance. It is unnecessary to say that the origin of congenital variation is one of the much discussed and still unsettled questions. At least two causes of congenital variations are commonly recognized, although opinions differ as to the relative importance of the rôle played by each. These causes are differences in the nutrition of the germ-plasm, and sexual reproduction. As to the former, it is evident that the germ-plasm in no two individuals, even father and son, has exactly identical nutritional opportunities. Since the life of one individual is not the exact counterpart of the life of another, the germ-plasm of one individual has a different nutrition from that of another. It would hence be strange, even although we regard the germ-plasm as relatively stable, if with succeeding generations there did not appear variations that are sufficient to give rise to unlikeness in relatives. Differences in the nutrition of the germ-plasm in different individuals are, therefore, a true cause of variations. As regards sexual reproduction, it must be remembered that a new individual is the product of two individuals, that the two individuals have descended along different genealogical lines, and hence that the two conjugating masses of germ-plasm are different in nature. It is only to be expected, therefore, that the resulting individual shall be different from the two contributing parents. Thus sexual reproduction is a true cause of variations.

Having outlined the main facts and principles of heredity, let us now review a few of the specific theories that have been of value in clearing the clouded atmosphere.

Darwin's Theory of Pangenesis.—Darwin's " Provisional Hypothesis of Pangenesis " was published in 1868 as chapter xxvii. of his work on *The Vari-*

ations of Animals and Plants under Domestication. It was the first of the modern theories to attempt to cover the whole ground of heredity; it was accompanied by a most exhaustive presentation and analysis of facts, and it stimulated abundant discussion and investigation. In Darwin's own words the hypothesis was formulated as follows: " It is universally admitted that the cells or units of the body increase by cell-division or proliferation, retaining the same nature, and that they ultimately become converted into the various tissues and substances of the body. But besides this means of increase I assume that the units [cells] throw off minute granules which are dispersed throughout the whole system; that these, when supplied with proper nutriment, multiply by self-division, and are ultimately developed into units like those from which they were originally derived. These granules may be called gemmules. They are collected from all parts of the system to constitute the sexual elements, and their development in the next generation forms a new being; but they are likewise capable of transmission in a dormant state to future generations, and may then be developed. Their development depends on their union with other partially developed or nascent cells which precede them in the regular course of growth. . . . . Gemmules are supposed to be thrown off by every unit, not only during the adult state, but during each stage of development of every organism; but not necessarily during the continued existence of the same unit. Lastly, I assume that the gemmules in their dormant state have a mutual affinity for each other, leading to their aggregation into buds or into the sexual elements. Hence, it is not the reproductive organs or buds which generate new organisms, but the units of which each individual is composed. These assumptions constitute the provisional hypothesis which I have called Pangenesis."

Since the cells of the body are represented by gemmules within the germ-cells, Darwin's theory is a theory of Preformation. It explains the facts of the regeneration of lost parts by the assumptions that the gemmules of the part in question are disseminated throughout the body and have only to unite with the nascent cells at the point of new growth. Pangenesis explains reversion, since gemmules may lie dormant in one generation and develop in the next. It explains congenital variation, since the mixture of maternal and paternal gemmules is plainly different from the two kinds taken separately. It explains how acquired variations may become congenital, since an altered part throws off altered gemmules, and by the collocation of these in the germ-cells the alteration may be transmitted. It thus allows the transmission of acquired characters.

Darwin's assumptions of gemmules and their behavior are pure assumptions, for which subsequent investigation has not provided a basis of facts. As we have seen, also, the inheritance of acquired characters is greatly in doubt, and, if they are heritable at all, they can be so only comparatively feebly. Besides these objections it was early found that, with the increase of knowledge of the facts of heredity, it was necessary to modify very materially the theory of Pangenesis. This has been ably done successively by

Galton,[1] Brooks,[2] and de Vries.[3] But neither the original theory nor its modifications have been generally accepted.

Weismann's Theory.—Since 1880, Professor Weismann [4] of Freiburg has published numerous essays upon heredity and allied subjects, in which, besides reviewing the views of others, he has developed in detail a new and elaborate theory of his own, that is the most ambitious attempt yet made to solve the problem of inheritance. In the course of their development Weismann's ideas have undergone some modification. Their leading features are as follows:

The essential hereditary substance, or germ-plasm, is the chromatin of the nucleus of the germ-cells. One of the fundamental tenets of Weismann's system is expressed by his own phrase, "the continuity of germ-plasm." By this is meant that the germ-plasm of one individual, instead of arising *de novo* in the individual by the collocation of multitudinous "gemmules" derived from the body-cells, originates directly from the germ-plasm of the parent, thence from that of the grandparent, and so on backward through all generations to the origin of all germ-plasms that took place simultaneously with the origin of sex—germ-plasm is continuous from individual to individual along any one line of descent. Weismann draws a sharp line between *germ-plasm* and *somatoplasm*, or body-plasm, which latter comprises all protoplasm that the body contains except the germ-plasm. Germ-plasm once originated continues from generation to generation; somatoplasm develops anew in each generation from germ-plasm by growth and differentiation, resulting in a loss of its specific germinal character. Germ-plasm is stable in composition; somatoplasm is variable. Germ-plasm, being passed on from parent to offspring, is immortal; somatoplasm dies when the individual dies. Weismann believes that "the germ-plasm possesses a fixed architecture, which has been transmitted historically" and which represents the parts of the future organism. It consists of material particles or hereditary units called *determinants,* each of which has a definite localized position within the germ-plasm. The determinants are suggestive of Darwin's gemmules, yet they are not the same, for, while gemmules were supposed to represent individual cells, determinants are representatives of cells or groups of cells that are variable from the germ onward. Determinants consist of definite combinations of simpler units, or *biophors,* which are the smallest particles that can exhibit vital phenomena. Below biophors there come in order of simplicity of material structure the molecules and the atoms of the physicist. Above biophors and determinants Weismann finds it necessary to assume the existence of higher units, named in order *ids* and *idants,* the former being groups of determinants, and actually visible as granules of chromatin, the latter being the chromosomes of the nucleus. Each

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[1] Francis Galton: "A Theory of Heredity," *Journal of the Anthropological Institute,* 1875.

[2] W. K. Brooks: *The Laws of Heredity,* 1883.

[3] H. de Vries: *Die Intracelluläre Pangenesis,* 1889.

[4] August Weismann: *Essays upon Heredity and Kindred Biological Problems,* authorized translation, vol. i., 1889; vol. ii., 1892; *The Germ-plasm,* authorized translation, 1893; *The Effect of External Influences upon Development,* the Romanes Lecture, 1894.

one of these various units is possessed of the fundamental vital properties of growth and multiplication by division. Such a complex system is Preformation in an extreme form. In fertilization idants of the sperm join with idants of the ovum, and the resulting segmentation nucleus consists of a mixture of paternal and maternal determinants. Within this mixture there exist in a potential state the primary constituents of a considerable number of forms which the future individual may assume. In ontogeny, or development of the individual, these primary constituents take two paths: some of the ids remain inactive and enter the germ-cells of the embryo for the production of future generations; other ids disintegrate into determinants, the determinants enter the embryonic cells that result from segmentation, and there themselves disintegrate and set free into the cytoplasm their constituent biophors; thus they determine the future character of the cells of the organism. The division of primary constituents into those that shall remain latent and those that shall become active is effected largely by the stimulation of external influences; hence, given several potential formations in the germ, external influences decide which one shall become the actual structure in the adult organism. Once set free and having become somatoplasm, neither the biophors nor the determinants are able to return to the germ-cells. In the adult, germ-plasm is never capable of reflecting in any way the characteristics of the somatoplasm which surrounds it on all sides. With its ancient ancestry it leads a charmed existence, largely independent of environmental changes. It follows that characters acquired by the adult are incapable of acquisition by the germ-plasm, and hence may not be transmitted. The *non-inheritance of acquired characters* is thus another of the fundamental tenets of Weismann's theory, and one about which he is most positive.

If these two principles of continuity of stable germ-plasm and non-inheritance of acquired characters be true, why are not all individuals in any one line of descent exactly like each other? How is congenital variation possible? In the first place, Weismann allows that germ-plasm, while eminently stable, is not absolutely so; it is subject to slight continual changes of composition resulting from inequalities in nutrition; and "these very minute fluctuations, which are imperceptible to us, are the primary cause of the greater deviations in the determinants which we finally observe in the form of individual variations." The accumulation of minute deviations may be aided greatly by sexual reproduction, or, to use Weismann's more exact term, which is equally applicable to the combination of sexual elements in sexual organisms and to the process of conjugation in the asexual forms, *amphimixis.* Given the infinitesimal beginning of a variation, the mingling of two lines of descent, with different past surroundings, may be a most powerful factor in strengthening the deviation and bringing it into recognition as a new character. Moreover, natural selection becomes here also potent as soon as the variation has assumed sufficient proportions to be seized upon by this important factor of evolution. In cases of reversion Weismann supposes the determinants to remain inactive in the germ-plasm for one or more generations and later to develop. The

theory accounts for the regeneration of lost parts by the assumption that the cells in the vicinity of the wound, by the proliferation of which the new part grows, contain, besides the active determinants that have given them their specific character, other determinants that are latent until the opportunity for regeneration arrives. Some cells do not possess such latent determinants, and hence some parts of a body are incapable of reproducing lost parts.

Such are the main features of Weismann's theory—a germ-plasm of highly complex architecture and independent of somatoplasm; continuity of germ-plasm and non-inheritance of acquired somatic characters tending to preserve the uniformity of the species; slight nutritional variation of germ-plasm and sexual reproduction tending to destroy that uniformity; the result is inherited resemblance and congenital variation. The theory is now being most actively discussed.

Theory of Epigenesis.—Among epigenesists no one theorp may be said to be pre-eminent. The main features of the epigenetic conception, already referred to, may be summarized as follows: The fertilized ovum is isotropous, *i. e.* all parts are essentially alike; germ-plasm probably consists of minute particles, but these particles do not represent definite cells or groups of cells of the adult; segmentation is a quantitative process; the early blastomeres are essentially alike, and any one of them, if isolated from the rest, may give rise to a whole organism, although under ordinary circumstances they react upon each other in bringing about the resultant individual; there is no predetermination, either in the germ-cells or in the segmenting ovum, of the ultimate form or function of the various constituent parts; morphological differentiation and physiological specialization are phenomena of comparatively late embryonic life, and the prospective character of any one cell, whether it is to be a muscle-cell, gland-cell, nerve-cell, or germ-cell, is determined by the influence of the surrounding cells and the surrounding physical and chemical conditions—"the prospective character of each cell is a function of its location." Extreme epigenetic views are not so numerous as those of preformation.[1]

The more moderate thinkers of the present time recognize truth in both preformation and epigenesis, and are endeavoring by experimental methods to determine how much share in the production of the characteristics of the offspring is to be ascribed to the original qualities of the germ-plasm and how much to the physical, chemical, and physiological phenomena of the immediate environment of the developing embryo. Such experimental work is performed at present upon the simpler and lower animals, mostly marine invertebrates, and has reference to the effect of changes in the composition of the water surrounding the embryo, the effects of various salts, of changes in temperature, of pressure, of electricity, etc., etc. Such work is now in its infancy, but it is doubtless destined to yield results of the highest value in an understanding of the true nature of heredity.

[1] The best statement of a moderate epigenetic theory is to be found in *Zeit- und Streitfragen der Biologie: I. Präformation oder Epigenesis?* O. Hertwig, 1894.

XIV. THE CHEMISTRY OF THE ANIMAL BODY.

Introduction.—Living matter contains hydrogen, oxygen, sulphur, chlorine, fluorine, nitrogen, phosphorus, carbon, silicon, potassium, sodium, calcium, magnesium, and iron. Abstraction of one of these elements means death to the organization. The compounds occurring in living matter may for the most part be isolated in the laboratory, but they do not then exhibit the properties of animate matter. In the living cell the smallest particles of matter are arranged in such a manner that the phenomena of life are possible. Such an arrangement of materials is called *protoplasm*, and anything which disturbs this arrangement results in sickness or in death. Somatic death may result from physical shock to the cell; or it may be due to the inability of the cell or the organism to remove from itself poisonous products which are retained in the body so affecting the smallest particles that functional activity is impossible. Pure chemistry adds much to our knowledge of physiology, but it must always be remembered that the conditions present in the beaker glass are not the conditions present in the living cell, physical and chemical results being dependent on surrounding conditions; hence the necessity and value of animal experimentation. From chemical changes, the physical activities, *i. e.* the motions characteristic of life, result. Hence the chemistry of protoplasm is the corner-stone of biology. The plan of this section is designed to consider the substances concerned in life in the order usually followed by chemical text-books.

THE NON-METALLIC ELEMENTS.

HYDROGEN, H = 1.

This gas is found as a constant product of the putrefaction of animal matter, and is therefore present in the intestinal tract. It is found in the expired air of the rabbit and other herbivorous animals, and in traces in the expired air of carnivorous animals, having first been absorbed by the blood from the intestinal tract. By far the greater amount of hydrogen in the animal and vegetable worlds, as well as in the world at large, occurs combined in the form of water, and it will be shown that the proteids, carbohydrates, and fats, characteristic of the organism, all contain hydrogen originally derived from water. In the atmosphere is found ammonia in traces, which holds hydrogen in combination, and this is a second source of hydrogen, especially for the construction of the proteid molecule.

Preparation.—(1) Through the electrolysis of water, by which one volume

of oxygen is evolved on the positive pole and two volumes of hydrogen on the negative.

(2) Through the action of zinc on sulphuric acid,[1]

$$Zn + H_2SO_4 = ZnSO_4 + H_2.$$
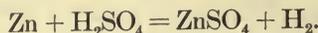
(3) Through putrefaction (by which is understood the change effected in organic matter through certain lower organisms, *bacteria*) hydrogen is liberated in the intestinal canal from proteid matter, and especially from the fermentation of carbohydrates:

$$C_6H_{12}O_6 = C_4H_8O_2 + 2CO_2 + 2H_2.$$
Sugar.   Butyric acid.
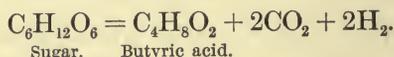
In putrefaction in the presence of oxygen the hydrogen formed immediately unites with oxygen, producing water ; hence, notwithstanding the enormous amount of putrefaction in the world, there is no accumulation of hydrogen in the atmosphere.

Both bacteria and an *enzyme* can liberate hydrogen by acting on calcium formate,

$$Ca (CHO_2)_2 + H_2O = CaCO_3 + CO_2 + 2H_2,$$

and this same reaction may be brought about by the action of metallic iridium, rhodium, or ruthenium on formic acid. An *enzyme* is a substance probably of proteid nature capable of producing change in other substances without itself undergoing apparent change (example, pepsin). Bunge[2] calls attention to the fact that the above reaction may be brought about by living cells (bacteria), by an organic substance (enzyme), and by an inorganic metal. This similarity of action between organized and unorganized material, between living and dead substances, is shown more and more conspicuously as science advances.

Properties.—Hydrogen burns in the air, forming water, and if two volumes of hydrogen and one of oxygen be ignited, they unite with a loud explosion. Hydrogen will not support respiration, but, mixed with oxygen, may be respired, probably being dissolved in the fluids of the body as an inert gas, without effect upon the organism. Hydrogen may pass through the intestinal tissues into the blood-vessels, according to the laws of diffusion, in exchange for some other gas, and may then be given off in the lungs. *Nascent hydrogen*—that is to say, hydrogen at the moment of generation—is a powerful reducing agent, uniting readily with oxygen (see p. 952).

Oxygen, O = 16.

Oxygen is found free in the atmosphere to the amount of about 21 per cent. by volume, and is found dissolved in water and chemically combined in arterial blood. It is swallowed with the food and may be present in the stomach, but it entirely disappears in the intestinal canal, being absorbed by respiratory exchange through the mucous membrane. It occurs chemically combined with metals so that it forms one-half the weight of the earth's crust ; it likewise occurs combined in water and in most of the materials forming animal and vegetable organisms. It is found in the blood in loose chemical

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[1] It is not within the scope of this work to give more than typical methods of laboratory preparation. For greater detail the reader is referred to works on general chemistry.

[2] *Physiologische Chemie*, 2d ed., 1889, p. 167.

combination as oxyhæmoglobin. It is present dissolved in the saliva, so great is the amount of oxygen furnished by the blood to the salivary gland; it is, however, not found in the urine or in the bile.

Preparation.—(1) Through the electrolysis of water (see Hydrogen).

(2) By heating manganese dioxide with sulphuric acid,

$$2MnO_2 + H_2SO_4 = 2MnSO_4 + 2H_2O + O_2.$$
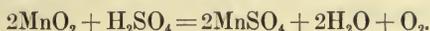
(3) By heating potassium chlorate,

$$2KClO_3 = 2KCl + 3O_2.$$
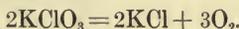
(4) By the action of a vacuum, or an atmosphere containing no oxygen, on a solution of oxyhæmoglobin,

$$Hb\text{-}O_2 = Hb + O_2.$$
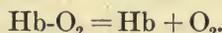
This latter is the method occurring in the higher animals. Any oxygen present in a cell in the body combines with the decomposition products formed there, consequently entailing in such a cell an oxygen *vacuum*, which now acts upon the oxyhæmoglobin of the blood-corpuscles in an adjacent capillary, *dissociating* it into oxygen and hæmoglobin.

(5) By the action of sunlight on the leaf of the plant, transforming the carbonic oxide and water of the air into sugar, and setting oxygen free,

$$6CO_2 + 6H_2O = C_6H_{12}O_6 + 6O_2.$$
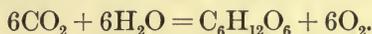
Properties.—All the elements except fluorine unite with oxygen, and the products are known as oxides, the process being called oxidation. It is usually accompanied by the evolution of energy in the form of heat, and often the energy liberated is sufficiently great to cause the production of light. The light of a candle comes from vibrating particles of carbon in the flame, which particles collect as lampblack on a cold plate. In pure oxygen combustion is more violent than in the air; thus, iron burns brilliantly in pure oxygen, while in damp air it is only very slowly converted into oxide (rust). This latter process is called slow combustion, and animal metabolism is in the nature of a slow combustion. In the burning candle has been noted the liberation of heat, and motion of the smallest particles: in the cell there is likewise oxidation, with dependent liberation of heat and motion of the smallest particles in virtue of which the cell is active. Phenomena of life are phenomena of motion, and the energy supplying this motion comes from chemical decomposition. The amount of oxidation in the animal is not increased in an atmosphere of pure oxygen, nor, within wide limits, is it affected by variations in atmospheric pressure, for oxygen is not the *cause* of decomposition. In putrefaction it is known that bacteria cause decomposition, and the products subsequently unite with oxygen. But the cause of the decomposition in the cell remains unsolved, it being only known that the decomposition-products after being formed unite with oxygen. So the quantity of oxygen absorbed by the body depends on the decomposition going on, not the decomposition on the absorption of oxygen. This distinction is fundamental (see further under Ozone and Peroxide of Hydrogen).

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By *reduction* in its simplest sense is meant the removal of oxygen wholly or in part from the molecule. Example: reduced hæmoglobin from oxy-hæmoglobin, iron from oxide of iron (Fe_2O_3). Reduction may likewise be accomplished by simple addition of hydrogen to the molecule, or by the substitution of hydrogen for oxygen. These two processes may be represented respectively by the reactions:

$$CH_3CHO + H_2 = CH_3CH_2OH.$$

Ethyl aldehyde.   Ethyl alcohol.

$$CH_3COOH + 2H_2 = CH_3CH_2OH + H_2O.$$

Acetic acid.   Ethyl alcohol.
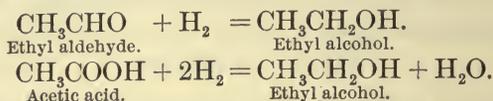
Ozone, O_3.—Ozone is a second form of oxygen possessing more active oxidizing properties than common oxygen. It is found in neighborhoods where large quantities of water evaporate, and after a thunder-storm.

Preparation.—(1) An induction current in an oxygen atmosphere breaks up some of the molecules present into atoms of nascent or "active" oxygen —O—, the powerful affinities of whose free bonds enter into combination with oxygen, $O = O$ to form

ozone, $\triangle$ $\begin{smallmatrix} O \\ O-O \end{smallmatrix}$.
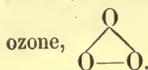
(2) Through the slow oxidation of phosphorus,

$$P_2 + 3H_2O + 2O_2 = 2H_3PO_3 + (-O-).$$
$$(-O-) + O_2 = O_3.$$
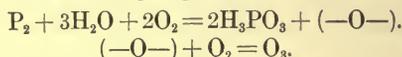
(3) On the positive pole in the electrolysis of water.

In each of the above cases ozone is formed by the action of nascent oxygen on oxygen.

Properties.—Ozone is a colorless gas, hardly soluble in water, and having the peculiar smell noted in the air after thunder-storms. Ozone has powerful oxidizing properties due to its third unstable atom of oxygen, oxidizing silver, which oxygen of itself does not. But ozone is not as oxidizing as nascent or "active" oxygen, which may convert carbon monoxide into dioxide, and nitrogen into nitrous acid. Ozone cannot occur in the cell, as any nascent oxygen formed would naturally unite not with oxygen, but with the more readily oxidizable materials of the cell itself. Ozone acts on an alcoholic solution of guaiacum, turning it blue; blood-corpuscles give the same reaction with guaiacum, hence it was thought that hæmoglobin converted oxygen into ozone. However, this test is not a test for ozone, but for "active" atomic oxygen, which is produced from the ozone and in the decomposing blood-corpuscle (see theory of Traube below, and that of Hoppe-Seyler under Peroxide of Hydrogen). Ozone converts oxyhæmoglobin into methæmoglobin.

Theory of Traube as to the Cause of Oxidation in the Body.—Indigo-blue dissolved in a sugar-solution gives up oxygen in the atomic state for the oxidation of sugar, and the solution becomes white. If shaken in the air the blue coloration reappears, owing to the absorption of oxygen by the indigo. Hence indigo has the power of splitting oxygen into atoms, and acts as an "oxygen-carrier" between the air and the sugar. Traube is of the opinion that an "oxygen-carrier" exists in the blood-corpuscles. Sugar is destroyed by standing in fresh defibrinated blood; serum alone does not effect this, nor does a solution of oxyhæmoglobin, but it may take place in the extract obtained by

the action of a 0.6 per cent. sodium-chloride solution on blood-corpuscles.[1] The action here has been described as that of *catalysis*, that is, an action in which some substance effects decomposition in another substance without permanent change in itself. In this case the substance in the blood-corpuscle, whatever it may be, is defined as an "oxygen-carrier," taking molecules of oxygen from oxyhæmoglobin and giving atomic oxygen for the oxidation of the sugar.

Old turpentine is highly oxidizing. This action was once believed to be due to absorbed ozone. If old turpentine be mixed with water and filtered, the aqueous extract has the same properties, due to the fact that an oxidized product which is soluble in water, gives off, under favorable conditions, atomic oxygen.[2]

Detection.—Moist strips of filter-paper soaked in starch-paste containing potassium iodide turn blue when exposed to the action of ozone, due to the liberation of free iodine, which colors the starch:

$$2KI + H_2O + O_3 = 2KOH + O_2 + 2I.$$
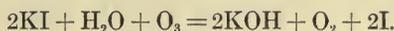
This liberation of iodine is likewise accomplished by chlorine, bromine, some nitrous oxides, and peroxide of hydrogen.

Water, H_2O.—Water is found on the earth in large quantities, and its vapor is a constant constituent of the atmosphere. It is a product of the combustion of animal matter, and occurs in expired air almost to the point of saturation. It is furthermore given off by the kidneys and by the skin. It is a necessary constituent of a living cell, and forms 67.6 per cent. of the weight of the human body (Moleschott). Removal of 5 to 6 per cent. of water from the body, as for example in cholera, causes the blood to become very viscid and to flow slowly, no urine is excreted, the nerves become excessively irritable, and violent convulsions result.[3]

Preparation.—(1) By passing an electric spark through a mixture of one volume of oxygen and two volumes of hydrogen.

(2) By the combustion of a food—as, for example,

$$C_6H_{12}O_6 + 12O = 6CO_2 + 6H_2O.$$
$$\text{Sugar.}$$
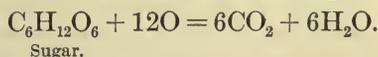
(3) *Distilled water* is made in quantity by boiling ordinary water and condensing the vapors formed in another vessel.

Properties.—Water is an odorless, tasteless fluid of neutral reaction, colorless in small quantities, but bluish when seen in large masses. It is a bad conductor of heat and electricity. It conducts electricity better when it contains salts. It is nearly non-compressible and non-expansible; thus in plant-life, through evaporation on the surface of the leaf, sap is continuously attracted from the roots of the tree. The solvent properties of water give to the blood many of its uses, soluble foods being carried to the tissues and soluble products of decomposition to the proper organs for elimination.

When water is absorbed by any substance the process is called *hydration*, as an example of which may be cited the change of calcium oxide into

[1] Read W. Spitzer: *Pflüger's Archiv*, 1895, Bd. 60, p. 307.
[2] N. Kowalewsky: *Centralblatt für die medicinische Wissenschaft*, 1889, p. 113.
[3] C. Voit: *Hermann's Handbuch*, 1881, Bd. vi., 1, p. 349.

hydroxide when thrown into water. When a substance breaks down into simpler bodies through absorption of water the process is called *hydrolysis* or *hydrolytic cleavage.* Thus cane-sugar may take up water and be resolved into a mixture of dextrose and levulose, which are called *cleavage-products.* So, likewise, starch and proteid are resolved into series of simpler bodies through hydrolytic cleavage—changes which take place in intestinal digestion. All forms of fermentation and putrefaction are characterized by hydrolysis (examples, p. 944), and hence complete drying prevents such processes. Alcoholic, butyric, and lactic fermentation are apparent though not real exceptions to the above. Alcoholic fermentation, for example, is usually represented by the reaction, $C_6H_{12}O_6 = 2C_2H_5OH + 2CO_2$, but the CO_2 is in fact united with water, and hence the true reaction should read,

$$C_6H_{12}O_6 + 2H_2O = 2C_2H_5OH + 2H_2CO_3.$$

Sugar.   Alcohol.
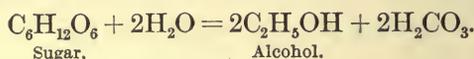
Drinking-water contains salts and air dissolved, giving it an agreeable taste. One does not willingly take distilled water on account of its tastelessness. Drinking large quantities of water produces a slight increase in the decomposition of proteid in the body.

Dry animal membranes and cells absorb water in quantities varying with the concentration and the quality of salts in the solution in which they are suspended (Liebig). This is called *imbibition.* Membranes will absorb a solution of potassium salts in greater quantity than of sodium salts, and so the potassium salts are found predominating in the cells, the sodium salts in the fluids of the body. A blood-corpuscle treated with distilled water swells because it can hold more distilled water than it can salt-containing plasma. A corpuscle placed in a 0.65 per cent. solution of sodium chloride (the physiological salt-solution) remains unchanged, for this corresponds in concentration to the plasma of the blood. If the corpuscle be placed in a strong solution of a salt it shrivels, because it cannot hold as much of that solution as it can one having the strength of the salts of the plasma. Oysters are often planted at the mouths of fresh-water rivers, since they imbibe more of the weaker solution and appear fatter. If salt be placed on meat and left to itself, a brine is formed around the meat, not on account of the hygroscopic properties of the salt, but because salt penetrates the tissues, which can then hold less water than they could before, and so water is forced out from the meat.

Different bodies require different quantities of heat to warm them to the same extent. The amount of heat required to raise the temperature of water is greater than that for any other substance. A *calorie* or heat-unit is the amount of heat required to raise 1 cubic centimeter of water from 0° to 1° C. The *specific heat* of the human body—that is, the amount of heat required to raise 1 gram 1° C.—is about 0.8 that of water. On the transformation of a substance from the solid to the liquid state, a certain amount of heat is absorbed, known as *latent heat.* To melt 1 gram of ice producing 1 gram of water at 0°, 79 calories are required, or sufficient to raise 1 gram of water from 0° to 79°. Upon the basis of these facts a determination may be made by means of the *ice-calorimeter* of the number of heat-units produced in the combustion. For example, 1 gram of sugar (dextrose) burned in an ice-chamber, melts 49.86 grams of ice. Since each gram required 79 calories to melt it, 3939 calories must have been produced altogether. If 1 gram of sugar be burned in the body, the heat produced is identically the same, and may be measured with great accuracy.[1]

In the transformation of water at 100° to steam at 100° there is a further absorption of

[1] M. Rubner: *Zeitschrift für Biologie,* 1893, Bd. 30, p. 73.

heat, the latent heat of steam. For 1 gram of water this absorption amounts to 536.5 calories. This property of water is of great value to life, for through the heat absorbed in the evaporation of sweat the temperature of the body is in part regulated.

Peroxide of Hydrogen, H_2O_2, is found in very small quantities in the air, in rain, snow, and sleet, and where there is oxidation of organic matter.

Preparation.—(1) By the action of sulphuric acid on peroxide of barium,

$$BaO_2 + H_2SO_4 = BaSO_4 + H_2O_2.$$
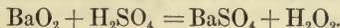
(2) Peroxide of hydrogen is a product of the oxidation of phosphorus, and generally exists wherever ozone is produced.

(3) Peroxide of hydrogen exists wherever nascent hydrogen acts on oxygen. It is therefore found mixed with hydrogen evolved at the negative pole in the electrolysis of water. This action happens in putrefaction, where the nascent hydrogen unites with any oxygen present, and the resulting H_2O_2 strongly oxidizes the organic matter through the free —O— atom liberated.[1]

Properties.—Peroxide of hydrogen is a colorless, odorless, bitter-tasting fluid, which decomposes slowly at 20° F., and with great violence at higher temperatures. It oxidizes where ordinary oxygen is ineffective; it is a powerful bleaching agent, and is used to produce blonde hair. It destroys bacteria. Blood-corpuscles brought into a solution of H_2O_2 bring about its rapid decomposition into water and atomic oxygen, whereby oxygen is evolved and oxyhæmoglobin is converted into methæmoglobin. If oxyhæmoglobin be brought into a putrefying fluid, the nascent hydrogen withdraws oxygen from combination to form H_2O_2, and then the atomic oxygen reacts on hæmoglobin to form methæmoglobin.[2] The formula for the peroxide is probably H—O—O—H. In certain cases peroxide of hydrogen has a reducing action.

Theory of Hoppe-Seyler[3] *to account for the Oxidation in the Body.*—This maintains that, as in putrefaction, hydrogen is produced in the decomposition of the cell, and acting on the oxygen present converts it into peroxide with its unstable atom, which then splits off as active oxygen and effects the oxidation of the substances in the cell. This theory is easier to reconcile with the fact that oxidation is dependent on the amount of decomposition (see p. 945) than is the theory of Traube.

Detection.—Solutions of H_2O_2 do not liberate iodine from potassium iodide immediately, but only on the addition of blood-corpuscles or of ferrous sulphate, which cause liberation of —O—, and then any starch present may be colored blue (see p. 947). Guaiacum is not affected by H_2O_2 unless blood-corpuscles or ferrous sulphate be added which make the oxygen active.

SULPHUR, S = 32.

Sulphur is built in the proteid molecule of the plant from the sulphates taken from the ground. It is found in albuminoids, especially in keratin. As taurin it occurs in muscle and in bile, as iron and alkaline sulphide in the

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[1] Hoppe-Seyler : *Zeitschrift für physiologische Chemie*, 1878, Bd. 2, p. 22.

[2] Hoppe-Seyler, *Op. cit.*, p. 26.

[3] *Pflüger's Archiv*, Bd. 12, p. 16, 1876. See also *Berichte der deutschen chemischen Gesellschaft*, Bd. 22, p. 2215.

feces, as sulphuretted hydrogen in the intestinal gas, as sulphate and other unknown compounds in the urine.

Detection.—If a sulphur compound be fused with sodium carbonate on charcoal, the sulphur will be reduced to sodium sulphide. The melted mass if placed with a drop of water on a silver coin leaves a black spot of silver sulphide.

Sulphuretted Hydrogen, H_2S.—This gas is found in the intestines, and pathologically in the urine.

Preparation.—(1) Action of hydrochloric or sulphuric acid on ferrous sulphide,

$$FeS + H_2SO_4 = FeSO_4 + H_2S.$$
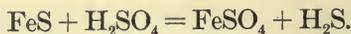
This same reaction takes place by treating feces (which contain FeS) with acid.

(2) From the putrefaction of proteids, and by boiling proteid with mineral acid.

Properties.—Sulphuretted hydrogen unites readily with the alkalies and with iron salts, forming sulphide; hence little H_2S is found in the intestinal tract. It is a strong poison when respired. It has been shown in frogs to enter into combination with oxyhæmoglobin to form sulph-hæmoglobin, and likewise rapidly kills the nerves.[1] Sulphuretted hydrogen diluted with hydrogen and introduced into the rectum of a dog produces symptoms of poisoning in one to two minutes (Planer). It has an offensive odor similar to foul eggs.

Detection.—If a piece of filter-paper soaked in acetate of lead be brought in contact with H_2S, it turns black, owing to the formation of sulphide of lead (PbS). Soluble sulphides in alkaline solution give with sodium nitro-prussiate, $Na_2Fe(CN)_5NO + 2H_2O$, an intense violet color, given also by acetone and aceto-acetic acid.

Sulphurous Acid, H_2SO_3.—This acid has been found in the urine of cats and dogs, and has been detected by Strümpell in human urine in a case of typhoid fever.

Sulphuric Acid, H_2SO_4.—This acid is found in the urine in combination with alkali (preformed sulphate), and with indol, skatol, cresol, and phenol (ethereal sulphates). It is found in the saliva of various gastropods.

Preparation.—(1) By oxidation of sulphur with nitric acid,

$$S + 2HNO_3 = H_2SO_4 + 2NO.$$
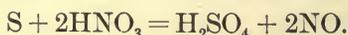
(2) By oxidation of sulphur-containing proteid.

Properties.—Sulphuric acid is a very powerful acid. It is produced in the body by the burning of the proteids (which contain 0.5 to 1.5 per cent. S), 80 per cent. or more being oxidized to acid, while the remainder appears in the urine in the unoxidized condition termed *neutral sulphur*. When proteid, fat, and starch free from ash is fed to dogs, they live only half as long as they would were they starving,[2] for, according to Bunge,[3] the sulphuric acid formed abstracts necessary salts from the tissue. (For further discussion of this see pp. 956 and 969).

Detection.—If 100 cubic centimeters of urine be treated with 5 cubic centimeters of

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[1] Harnack: *Archiv für experimentelle Pathologie und Pharmakologie*, 1894, Bd. 34, p. 156.

[2] J. Foster: *Zeitschrift für Biologie*, 1873, Bd. 9, p. 297.

[3] *Physiologische Chemie*, 2d ed., 1889, p. 104.

hydrochloric acid and barium chloride be added, the *preformed* sulphuric acid is precipitated as barium sulphate ($BaSO_4$), which may be washed, dried, and weighed. If 100 cubic centimeters of urine be mixed with an equal volume of a solution containing barium chloride and hydrate, filtered, and one-half the filtrate ($= 50$ cubic centimeters of urine, now free of *preformed* sulphate) be strongly acidified with hydrochloric acid and boiled, the ethereal sulphates will be broken up, and the resulting precipitate of barium sulphate will correspond to the *ethereal* sulphuric acid. To determine the *neutral* sulphur, evaporate the urine to dryness, fuse the residue with potassium nitrate (KNO_3), which oxidizes all the sulphur to sulphate, take up with water and hydrochloric acid, add barium chloride, and the precipitate ($BaSO_4$) represents the total sulphur present. Deduct the amount belonging to sulphuric acid, previously determined, and the remainder represents the neutral sulphur.

METABOLISM OF SULPHUR.—The total amount of sulphur in the urine runs proportionally parallel with the amount of nitrogen; that is to say, the amount is proportional to the amount of proteid destroyed. The amount of ethereal sulphate is dependent upon the putrefactive production of indol, skatol, phenol, and cresol in the intestinal canal, which on absorption form a synthetical combination with the traces of sulphate in the blood. Concerning neutral sulphur it is known that taurin is one source of it. If taurin be fed directly, the amount of neutral sulphur in the urine increases (Salkowski), and in a dog with a biliary fistula the neutral sulphur decreases but does not entirely disappear.[1] In a well-fed dog with a biliary fistula Voit[2] found the quantity of sulphur in the bile to be about 10 to 13 per cent. of that in the urine. This biliary sulphur (taurin) is normally reabsorbed, as the quantity of sulphur in the feces (FeS, Na_2S) is small and derived principally from proteid putrefaction. The amount of neutral sulphur in the urine is greatest under a meat diet, least when fat or gelatin is fed; the sulphur of gelatin burns apparently to sulphuric acid.[3] The neutral sulphur of the urine includes potassium sulphocyanide (originally derived from the saliva), likewise a substance which on treatment with calcium hydrate yields ethyl sulphide, $(C_2H_5)_2S$,[4] and there are present other unknown compounds. When an animal eats proteid and neither gains nor loses the same in his body, the amount of sulphur ingested is equal to the sum of that found in the urine and feces. If sulphur be eaten it partially appears as sulphate in the urine. Sulphates eaten pass out through the urine. They play no part in the life of the cell.

CHLORINE, $Cl = 35.5$.

Free chlorine is not found in the organization, and when breathed it vigorously attacks the respiratory mucous membranes. Chlorine is found combined in the body as sodium, potassium, and calcium chloride, as hydrochloric acid, and it is said to belong to the constitution of pepsin.[5]

[1] Kunkel: *Archiv für die gesammte Physiologie*, 1877, Bd. 14, p. 353.
[2] *Zeitschrift für Biologie*, 1894, Bd. 30, p. 554.   [3] Voit, *Op. cit.*, p. 537.
[4] J. J. Abel: *Zeitschrift für physiologische Chemie*, 1894, Bd. 20, p. 253.
[5] E. O. Schoumow-Simanowski: *Archiv für exper. Pathologie und Pharmakologie*, 1894, Bd. 33, p. 336.

Hydrochloric Acid, HCl, is found to a small extent in the gastric juice.

Preparation.—(1) If sunlight acts on a mixture of equal volumes of chlorine and hydrogen, they unite with a loud explosion.

(2) By the action of strong sulphuric acid on common salt,

$$2NaCl + H_2SO_4 = Na_2SO_4 + 2HCl.$$
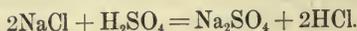
(3) By the action of primary acid phosphate of sodium on common salt,

$$NaH_2PO_4 + NaCl = Na_2HPO_4 + HCl.$$
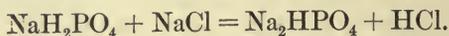
This, according to Maly, represents the process in the cells of the gastric glands.

Properties.—Hydrochloric acid readily unites with most metals, forming chlorides. It causes a gelatinization of the proteids and seems to unite with them chemically. Such gelatinization is a necessary forerunner of peptic digestion. The cleavage products of peptic digestion (peptones, proteoses, etc.) combine with more hydrochloric acid than the original more complex proteid.[1] Hydrochloric acid of the strength of the gastric juice (0.2 per cent.) inverts cane-sugar at the temperature of the body, and inhibits the action of bacteria. Hydrochloric acid is indisputably derived from decomposition of chlorides in the secreting cells of the stomach. It has been shown that the excretion of common salt in the urine is decreased during those hours that the stomach is active, while the alkalinity of the urine increases. If, in a dog with a gastric fistula, the mucous membrane of the stomach be stimulated and the gastric juice be removed as soon as formed, the urine becomes strongly alkaline with sodium carbonate (the excess of Na liberated taking this form) while the chlorides may entirely disappear from the urine.[2] Respiration in an atmosphere containing 0.5 per cent. HCl gas becomes very uncomfortable after twelve minutes.[3]

Detection.—Hydrochloric acid and the chlorides give with silver nitrate a white precipitate of silver chloride, insoluble in nitric acid, very soluble in ammonia. If the bases (K, Na, Ca, Mg, Fe) of gastric juice and then the acid radicals (Cl and P_2O_5) be determined, after uniting by calculation phosphoric anhydride with the proper bases, then chlorine with the rest of the bases, there still remains an excess of chlorine which could only have belonged to hydrochloric acid present. To detect free hydrochloric acid, put three or four drops of a saturated alcoholic solution of tropæolin 00 in a small white porcelain cover, add to this an equal quantity of gastric juice, evaporate slowly, and the presence of hydrochloric acid is shown by a beautiful violet color, not given by any organic acid.[4] Günzburg's reagent consisting of phloroglucin and vanillin in alcoholic solution, warmed (as above) with gastric juice containing free hydrochloric acid, gives a carmine-red mirror on the porcelain, not given by an organic acid.[5]

CHLORINE IN THE BODY is ingested as chloride, and leaves the body as such, principally in the urine, likewise through the sweat and tears, and in traces in the feces.

[1] Chittenden: *Cartwright Lectures on Digestive Proteolysis,* 1895, p. 52.

[2] E. O. Schoumow-Simanowski: *Archiv für exper. Pathologie und Pharmakologie,* 1894, Bd. 33, p. 336.

[3] Lehmann: *Archiv für Hygiene,* Bd. 5, p. 1.

[4] Boas: *Deutsche medicinische Wochenschrift,* 1887, No. 39.

[5] Günzburg: *Centralblatt für klinische Medicin,* 1887, No. 40.

BROMINE, Br = 80.

Salts of bromine are found in marine plants and animals, but their physiological importance has not been established. Bromine is a fluid of intensely disagreeable odor, whose vapors strongly attack the skin, turning it brown, and likewise the mucous membranes of the respiratory passages.

Hydrobromic Acid, HBr, may be prepared by the action of water on phosphorus tribromide;

$$PBr_3 + 3H_2O = 3HBr + H_3PO_3.$$
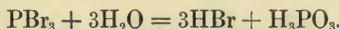
It is a colorless gas of penetrating odor. If sodium bromide be given to a dog in the place of sodium chloride, fifty per cent. and more of the hydrochloric acid may be supplanted by hydrobromic acid in the gastric juice.[1]

IODINE, I = 127.

Like bromine, the salts of iodine are found in many marine plants and animals, especially in the *algæ*. It is found in the thyroid gland. Iodine is prepared in metallic-looking plates, almost insoluble in water, but soluble in alcohol (tincture of iodine). Iodine is still more strongly corrosive in its action on animal tissue than is chlorine or bromine, and is an antiseptic and disinfectant. A slight trace of free iodine turns starch blue.

Hydriodic Acid, HI, is prepared like hydrobromic acid, by the action of water on tri-iodide of phosphorus. An aqueous solution of hydriodic acid introduced into the stomach is absorbed, and shortly afterward iodine, as alkaline iodide, may be detected in the urine. On administration of sodium iodide to a dog with his food, only very little hydriodic acid appears in the gastric juice.[2]

CIRCULATION IN THE BODY.—Iodine or iodides given are rapidly eliminated in the urine, in smaller amounts in saliva, gastric juice, sweat, milk, etc. It is noticed that for weeks after the administration of the last dose of potassium iodide, traces of iodine are found in the saliva, and none in the urine. The explanation lies in the presumption that iodine has been united with proteid to a certain extent, and appears in such secretions as saliva, which contains materials derived from proteid through glandular manufacture.[3] A similar explanation avails in the case of Drechsel's[4] discovery that, in patients who have been treated with iodides, iodine may be detected in the hair (the keratin of hair being derived from other proteid bodies.) Baumann[5] has recently announced the discovery of an organic compound of iodine occurring in the thyroid gland and containing as much as 9.3 per cent. of iodine. This *thyro-iodin* is the effective principle, or at least one of the effective principles, of the thyroid gland.[6] Whether free iodine or hydriodic acid is liberated in the tissues from ingested iodides is a disputed point.

FLUORINE, F = 19.

Fluorine is found in the bones and teeth, in muscle, brain, blood, and in all investigated tissues of the body, though in small quantities. In one liter of milk 0.0003 gram of fluorine have been detected.[7] Fluorine is found in plants, and in soil without fluorine plants do not flourish. It seems to be a necessary constituent of protoplasm. Free fluorine is a gas which cannot be preserved, as it unites with any vessel in which it is prepared.

[1] Nencki and Schoumow-Simanowski: *Archiv für exper. Pathologie und Pharmakologie,* 1895, Bd. 34, p. 320.   [2] Nencki and Schoumow-Simanowski, *loc. cit.*

[3] Schmiedeberg: *Grundriss der Arzneimittellehre,* 2d ed., 1888, p. 197.

[4] *Centralblatt für Physiologie,* 1896, Bd. 9, p. 704.

[5] *Zeitschrift für physiologische Chemie,* 1895, Bd. 21, p. 319.

[6] See Drechsel: *Centralblatt für Physiologie,* 1896, Bd. 9, p. 705.

[7] G. Tammann: *Zeitschrift für physiologische Chemie,* 1888, Bd. 12, p. 322.

Hydrofluoric Acid, HF, is prepared by heating a fluoride with concentrated sulphuric acid, in a platinum or lead dish,

$$CaF_2 + H_2SO_4 = CaSO_4 + 2HF.$$

Properties.—Hydrofluoric acid is a colorless gas, so powerfully corrosive that breathing its fumes results fatally. Its aqueous solutions are stable, but can be kept only in vessels of platinum, gold, lead, or india-rubber. It etches glass, uniting to form volatile silicon fluoride,

$$SiO_2 + 4HF = SiF_4 + 2H_2O.$$
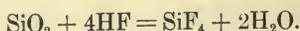
Detection.—If silicon be absent from the substance to be tested, the above reaction may be used, and if the glass be etched, after treating the substance with sulphuric acid, fluorine is present. In the organism silicon is found, and the method of detection is different. The principle of the method depends on the fact that SiF_4 in contact with water forms silicic acid (H_4SiO_4), and hydrofluor-silicic acid (H_2SiF_6). If the ash of the organ be mixed with powdered silica (SiO_2), transferred to a flask, mixed with concentrated sulphuric acid, then heated, and if a current of dry air remove the SiF_4 from the flask through a tube into water, the slightest trace of fluorine is proven by the appearance of a whitish cloud of silicic acid at that part of the tube where SiF_4 first comes in contact with moisture. This may be noted when 0.0001 gram of fluorine is present.[1]

CIRCULATION IN THE BODY.—Tappeiner and Brandl[2] have shown, on feeding sodium fluoride (NaF) to a dog in doses varying between 0.1 and 1 gram daily, that the fluorine fed was not all recoverable in the urine and feces, but was partially stored in the body. On subsequently killing the dog, fluorine was found in all the organs investigated, and was especially found in the dry skeletal ash to the extent of 5.19 per cent. reckoned as sodium fluoride. From the microscopic appearance of the crystals seen deposited in the bone, the presence of calcium fluoride was concluded. In this form it normally occurs in bones and teeth.

NITROGEN, N = 14.

Free nitrogen constitutes 79 per cent. of the volume of atmospheric air. It is found dissolved in the fluids and tissues of the body to about the same extent as distilled water would dissolve it. It is swallowed with the food, may partially diffuse through the mucous membrane of the intestinal tract, but forms a considerable constituent of any final intestinal gas. It is found in the atmosphere combined as ammonium nitrate and nitrite, which are useful in furnishing the roots of the plant with material from which to build up proteid. Bacteria upon the roots of certain vegetables combine and assimilate the free nitrogen of the air (Hellriegel and Willforth). Cultures of *algæ* do the same.[3]

Preparation.—(1) By abstraction of oxygen from air through burning phosphorus in a bell jar over water, pentoxide of phosphorus being formed, which dissolves in the water and almost pure nitrogen remains.

(2) By heating nitrite of ammonium,

$$NH_4NO_2 = 2N + 2H_2O.$$
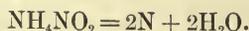
Properties.—Nitrogen is especially distinguished by the absence of chemical affinity for other elements. It does not support combustion, and in it both a

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[1] Tammann, *loc. cit.*   [2] *Zeitschrift für Biologie*, 1892, Bd. 28, p. 518.
[3] P. Kossowitch: *Botanische Zeitung*, 1894, Jahrg. 50, p. 97.

flame and animal life are extinguished, owing to lack of oxygen. It acts as a diluent of atmospheric oxygen, thereby retarding combustion, but on higher animal life it is certainly without direct influence.

Ammonia, NH_3, is found in the atmosphere as nitrate and nitrite to the extent of one part in one million. It is found in the urine in small quantities, is a constant product of the putrefaction of animal matter, and is a product of trypsin proteolysis.

Preparation.—(1) Through the action of nascent hydrogen on nascent nitrogen. This may be brought about by dissolving zinc in nitric acid,

$$3Zn + 6HNO_3 = 3Zn(NO_3)_2 + 6H.$$
$$10H + 2HNO_3 = 6H_2O + 2N.$$
$$N + 3H = NH_3.$$
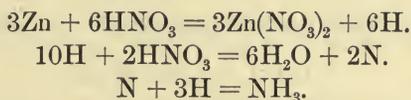
Ammonia is produced in a similar way in the dry distillation of nitrogenous organic substances in absence of oxygen, being therefore a by-product in the manufacture of coal-gas. In putrefaction nascent hydrogen acts on nascent nitrogen, producing ammonia, which in the presence of oxygen becomes oxidized to nitrate and nitrite, or in the presence of carbonic oxide is converted into ammonium carbonate. Ammonium nitrite is likewise formed on burning a nitrogenous body in the air, in the evaporation of water, and on the discharge of electricity in moist air,

$$2N + 2H_2O = NH_4NO_2.$$
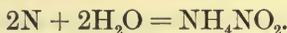
At the same time a small amount of nitrate is formed in the above three processes,

$$2N + 2H_2O + O = NH_4NO_3.$$

Hence these substances find their way into every water and soil, and furnish nitrogen to the plant. The value of decaying organic matter as a fertilizer is likewise obvious.

Properties.—Ammonia is a colorless gas of pungent odor. It readily dissolves in water and in acids, entering into chemical combination, the radical NH_4 appearing to act like a metal with properties like the alkalies, and its salts will be described with them. Very small amounts of ammonia instantly kill a nerve, but upon muscular substance it acts first as a stimulant, provoking contractions.

Detection.—On warming an ammonium salt with sodium hydrate, ammonia is set free, recognizable by its smell, by the fact that it turns turmeric paper brown, and that even in smallest traces it gives a yellow coloration, or, in greater amounts, a reddish precipitate in Nessler's reagent (mercuric iodide dissolved in potassium iodide and potassium hydrate).

AMMONIA IN THE BODY.—If it be agreed with Hoppe-Seyler that normal decomposition in the tissues is analogous to putrefaction, then nascent hydrogen acting on nascent nitrogen in the cell produces ammonia, which in the presence of carbonic acid becomes ammonium carbonate, and in turn may be converted into urea by the liver. If acids (HCl) be fed to carnivora (dogs) the amount

of ammonia present in the urine is increased, which indicates that an amount of ammonia usually converted into urea has been taken for the neutralization of the acid.[1] In a similar manner acids formed from decomposing proteid may be neutralized (see pp. 950 and 993).

The *ammoniacal fermentation* of the urine consists in the decomposition of urea into ammonium carbonate by the *micrococcus urinæ*, the urine becoming alkaline.

Compounds of Nitrogen with Oxygen.—There are various oxides of nitrogen, the higher ones being powerfully corrosive, and some of these unite with water to form acids, of which nitric acid (HNO_3) is the strongest. Only nitrous and nitric oxides are of physiological interest.

Nitrous Oxide, N_2O, likewise called "laughing-gas," is prepared by heating ammonium nitrate,

$$NH_4NO_3 = N_2O + 2H_2O.$$
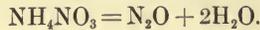
It supports ordinary combustion almost as well as pure oxygen, but it will not sustain life. Mixed with oxygen it may be respired, producing a state of unconsciousness preceded by hysterical laughter.

Nitric Oxide, NO, is prepared by dissolving copper in nitric acid,

$$3Cu + 8HNO_3 = 3Cu(NO_3)_2 + 4H_2O + 2NO.$$
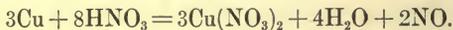
Contact with oxygen converts it into peroxide of nitrogen (NO_2), which is an irritating irrespirable gas of reddish color. Nitric oxide in blood first unites with the oxygen of oxyhæmoglobin, forming the peroxide (NO_2), and then the nitric oxide combines with hæmoglobin, forming a highly stable compound, nitric-oxide hæmoglobin (Hb-NO).

NITROGEN IN THE BODY.—Nitrogen is taken into the body combined in the great group of proteid substances, which are normally completely absorbed by the intestinal tract. It passes from the body in the form of simple decomposition-products, in larger part through the urine, but likewise through the juices which pour into the intestinal canal. The unabsorbed residues of these latter juices, mixed with intestinal epithelia constitute in greater part the *feces.*[2] An almost insignificant amount of nitrogen is further lost to the body through the hair, nails, and epidermis, but, generally speaking, the sum of the nitrogen in the urine and feces corresponds to the proteid decomposition for the same time (1 gram N = 6.25 grams proteid). When the nitrogen of the proteid eaten is equal in quantity to the sum of that in the urine and feces, the body is said to be in *nitrogenous equilibrium.* When the ingested nitrogen has been larger than that given off, proteid has been added to the substance of the body; when smaller, proteid has been lost. These propositions were established by Carl Voit.

A small amount of urea and other nitrogenous substances may be excreted in profuse sweating. Proteid nitrogen never leaves the body in the form of free nitrogen or of ammonia. That ammonia is not given off by the lungs may be demonstrated by performing tracheotomy on a rabbit, and passing the expired air first through pure potassium hydrate (to absorb CO_2) and then through Nessler's reagent. The experiment may be continued for hours with negative result.[3]

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[1] Fr. Walther: *Archiv für exper. Pathologie und Pharmakologie,* 1877, Bd. 7, p. 164.

[2] Menichanti and Prausnitz: *Zeitschrift für Biologie,* 1894, Bd. 30, p. 353.

[3] Bachl: *Zeitschrift für Biologie,* 1869, Bd. 5, p. 61.

PHOSPHORUS, P = ·32.

Phosphorus is found combined as phosphate in the soil; it is necessary to the development of plants. As phosphate it is present in large quantity in the bones, and is found also in all the cells, tissues, and fluids of the body, probably in loose chemical combination with the proteid molecule. It is present in nuclein, protagon, and lecithin.

Preparation.—Phosphorus was first prepared by igniting evaporated urine,

$$3NaH_2PO_4 + 5C = 3H_2O + 5CO + 2P + Na_3PO_4.$$
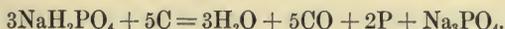
In a similar way it may be obtained by chemical treatment of bones. The vapors of phosphorus may be condensed by passing them under water, where at a temperature of 44.4° it melts and may be cast into sticks.

Properties.—Phosphorus is a yellow, crystalline substance, soluble in oils and carbon disulphide. It is insoluble in water, in which it is kept, since in moist air it gives off a feeble glowing light, accompanied by white fumes of phosphorous acid (H_3PO_3) and small amounts of ammonium nitrate, peroxide of hydrogen, and ozone, to which latter the peculiar odor is ascribed. Phosphorus ignites spontaneously at a temperature of 60°, and this may be produced by mere handling, the resulting burns being severe and dangerous. This form of phosphorus is poisonous, but if it be heated to 250° in a neutral gas (nitrogen) it is changed into red phosphorus, which has different properties and is not poisonous.

Phosphorus-poisoning.—On injecting phosphorus dissolved in oil into the jugular vein, embolisms are produced by the oil in the capillaries of the lungs, the expired air contains fumes of phosphorous acid, and the lungs glow when cut out (Magendie). If the phosphorus oil be injected in the form of a fine emulsion, embolism is avoided,[1] and the fine particles of phosphorus are generally distributed throughout the circulation. On autopsy of a rabbit after such injection in the femoral vein, all the organs and blood-vessels glow on exposure to the air.[2] If two portions of arterial blood be taken, and one of them be mixed with phosphorus oil, and they be let stand, both portions become venous in the same time.[3] Hence phosphorus in blood, as in water, is not readily oxidized. Persons breathing vapor of phosphorus acquire phosphorus-poisoning. What the direct action of phosphorus is, is unknown, but the results are most interesting. To understand the results it must be made clear that proteid in decomposing in the body splits up into a *nitrogeneous* portion which finds its exit through the urine and feces, and a *non-nitrogenous* portion which is resolved into carbonic oxide and water, just as are the sugars and the fats. This carbonic acid is given off, for the most part, through the lungs. Now if a starving dog, which lives on his own flesh and fat, be poisoned with phosphorus, the proteid decomposition as indicated by the nitrogen in the urine is largely increased, while the amount of carbonic acid given off and oxygen absorbed are largely decreased; on post-mortem examination the organs are found to contain excessive quantities of fat. We have here presumptive evidence that a part of the proteid molecule usually completely oxidized has not been burned,

[1] L. Hermann: *Pflüger's Archiv*, 1870, Bd. 3, p. 1.
[2] H. Meyer: *Archiv für exper. Pathologie und Pharmakologie*, 1881, Bd. 14, p. 327.
[3] Meyer, *Op. cit.*, p. 329.

but has been converted into fat.[1]   Similar results are characteristic of arsenic and antimony poisoning, and of yellow atrophy of the liver.

Detection.—If any organ containing phosphorus be boiled with water in a flask with a long upright tube, a ring of luminous phosphorus will condense at a certain point of the tube.

Compounds of Phosphorus with Oxygen.—Of these compounds three oxides and several acids exist, but only meta- and orthophosphoric acid need attention here.

Phosphorus Peroxide, P_2O_5, is a white powder, which rapidly absorbs moisture; it is produced by burning phosphorus in dry air.

Metaphosphoric Acid, HPO_3, is said to occur combined in nuclein.

Preparation.—(1) By dissolving P_2O_5 in cold water,

$$P_2O_5 + H_2O = 2HPO_3.$$
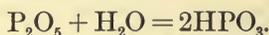
(2) By fusing phosphoric acid,

$$H_3PO_4 = HPO_3 + H_2O.$$

It is converted slowly in the cold, rapidly on heating, into phosphoric acid. Crystalline it forms ordinary glacial phosphoric acid.   Metaphosphoric acid precipitates proteid from solution, yielding a body having the properties of nuclein,[2] but this has been denied.[3]

Orthophosphoric Acid, H_3PO_4.—Salts of this acid constitute all the inorganic compounds of phosphorus in the body, and are called phosphates.

Preparation.—(1) By heating solutions of metaphosphoric acid,

$$HPO_3 + H_2O = H_3PO_4.$$

(2) By treating bone-ash with sulphuric acid,

$$Ca_3(PO_4)_2 + 3H_2SO_4 = 3CaSO_4 + 2H_3PO_4.$$
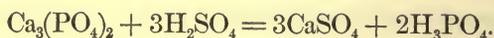
Properties.—On evaporation of the liquors obtained above, the acid separates in colorless hygroscopic crystals.

Phosphoric acid forms different salts according as one, two, or three atoms of hydrogen are supplanted by a metal.   Thus there exist primary sodium or calcium phosphates, NaH_2PO_4 and $Ca{<}{H_2PO_4 \atop H_2PO_4}$; the secondary phosphates, Na_2HPO_4 and $CaHPO_4$; and the tertiary phosphates, Na_3PO_4 and $Ca_3(PO_4)_2$.   On account of their reaction to litmus these salts have been falsely called acid, neutral, and basic, but the secondary salts are, chemically speaking, acid salts.

The bones contain a large quantity of tertiary phosphate of calcium; the fluids and cells of the body contain likewise the primary and secondary phosphates, while to primary sodium phosphate carnivorous urine mainly owes its acid reaction.

In speaking of the ash of protoplasm, Nencki[4] advocates the idea of separate combinations of the base and acid radicles with the proteid molecule, as, for

[1] J. Bauer: *Zeitschrift für Biologie*, 1871, Bd. 7, p. 63.
[2] L. Liebermann: *Berichte der deutschen chemischen Gesellschaft*, Bd. 22, p. 598.
[3] Salkowski: *Pflüger's Archiv*, 1094, Bd. 59, p. 245.
[4] *Archiv für exper. Pathologie und Pharmakologie*, 1894, Bd. 34, p. 334.

example, the separate union of potassium with proteid and of phosphoric acid with proteid, in the functionally active cell. However combined, phosphoric acid is necessary for the organism.

Detection.—A solution of phosphate treated with a magnesium salt dissolved in ammonia containing ammonium chloride, gives a fine crystalline precipitate of magnesium-ammonium phosphate, which on ignition loses ammonia and is converted into magnesium pyrophosphate.

PHOSPHORUS IN THE BODY.—The principal source of supply is derived from the phosphates of the alkalies and alkaline earths in the foods; it may be absorbed in organic combinations in nuclein, casein, and caseoses; and it may further be absorbed as glycerin phosphoric acid, which is an intestinal decomposition product of lecithin [1] and probably also of protagon. Phosphorus leaves the body almost entirely in the form of inorganic phosphate, the only exception being glycerin phosphoric acid, which has been detected in traces in the urine. In man and carnivora the soluble primary and secondary phosphates of the alkalies are found in the urine, together with much smaller amounts of the less soluble primary and secondary phosphates of the alkaline earths. There is likewise, even during hunger, a continuous excretion of tertiary phosphate of calcium, magnesium, and iron in the intestinal tract. In herbivora the excretion is normally into the intestinal tract, and no phosphates occur in the urine. This is because herbivora eat large quantities of calcium salts which bind the phosphate in the blood, and they likewise eat organic salts of the alkalies, which become converted into carbonate and appear in the urine as acid carbonates; such a urine has no solvent action on calcium phosphate.[2] In a similar manner a great reduction of phosphate in the urine of man may be effected by feeding alkaline citrate and calcium carbonate, the first to furnish the more alkaline reaction to blood and urine, the second to bind the phosphate in the blood. The more alkaline reaction itself is insufficient to prevent the appearance of phosphates in the urine.[3] On the other hand, starving herbivora, or herbivora fed with animal food, give urines acid from primary phosphate.[4]

Excreted phosphates may be originally derived from the phosphates of the bones, or from phosphates arising from the oxidation of nuclein, protagon, and lecithin, but by far the greater quantity is derived from the food, or from proteid metabolism. In a starving dog, which feeds on its own proteid, it was found that a ratio existed between nitrogen and phosphoric acid in the urine as 6.4 : 1, which approximates that in muscle, *i. e.* 7.6 : 1. On feeding meat till nitrogenous equilibrium was established, the ratio became 8.1 : 1.[5] On addition of proteid to the body, a proportionate amount of phosphoric acid is retained for the new protoplasm, while on destruction of proteid the phosphoric acid corresponding to it is eliminated. The larger excretion of phosphoric acid

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[1] Bókay: *Zeitschrift für physiologische Chemie*, 1877–78, Bd. 1, p. 157.
[2] J. Bertram: *Zeitschrift für Biologie*, 1878, Bd. 14, p. 354. [3] *Op. cit.*, p. 354.
[4] Weiske: *Ibid.*, 1872, Bd. 8, p. 246.
[5] E. Bischoff: *Ibid.*, 1867, Bd. 3, p. 309.

during hunger shown in the ratio above, has been ascribed to the decomposition of the bones.[1] Thus Munk found on Cetti, who lived many days without food, a ratio as low as 4.5:1. In starvation the brain and nerves do not decrease in weight, so the protagon can hardly yield any great amount of phosphoric acid (Voit). Casein and other nucleo-albumins, when fed, are oxidized and furnish phosphoric acid for the urine.

CARBON, C = 12.

This element is found combined in every organism, and in many decomposition-products of organized matter. Elementary carbon occurs as lampblack, diamond, and graphite, the two latter having their origin from the action of high heat on coal. Carbon occurs combined in coal, petroleum, and natural gas, which are all products of the decomposition of wood out of contact with the air. Further it is found in vast masses, principally consisting of calcium carbonate, having their origin from sea-shells. The maintenance of life depends, as will be shown, on the small percentage of carbon dioxide which is contained in the atmosphere. Lavoisier believed that compounds of carbon were all products of life, formed under the influence of a "vital force," which was a property of the cell. It is now known that almost every constituent of the cell may be prepared from its elements in the laboratory without the aid of any "vital force" whatever. Notwithstanding its loss of strict scientific significance, the old term "organic" for a carbon compound is still in vogue, and conveniently describes a large number of bodies which are treated under the head of "organic chemistry," while the term "inorganic" is applied to the rest of the chemical world.

Elementary Carbon.—This burns only at a high heat. It is unaffected by the intestinal tract. This is shown by the fact that diamonds have been stolen by swallowing them, and that finely divided particles of lampblack pass unchanged and unabsorbed to the feces, coloring them black (proof that the intestinal canal does not absorb solid particles). If lampblack be eaten with a meal its appearance in the feces may be used as a demarcation line between the feces belonging to the period before the meal, and the period subsequent to it. Carbon unites directly with hydrogen, oxygen, and sulphur only.

Carbon Monoxide, CO.—This gas is a product of the incomplete combustion of carbon, is present in illuminating gas, and burns on ignition to carbon dioxide. It is usually prepared by heating oxalic acid with sulphuric acid,

$$\left. \begin{array}{l} COOH \\ | \\ COOH \end{array} \right. = H_2O + CO_2 + CO,$$
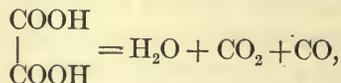
the carbon dioxide being removed by passing through calcium hydroxide.

Properties.—A colorless, odorless gas. Inspired, it unites with the blood to form a carbon-monoxide hæmoglobin (Hb-CO). This is a very stable bright-red compound which may even be boiled without decomposing. Ani-

[1] See Voit: *Hermann's Handbuch*, 1881, vi. 1, p. 79.

mals poisoned with CO die from want of oxygen, since the latter cannot displace the carbon monoxide from combination with hæmoglobin.

Carbon Dioxide, CO_2.—This is the highest oxidation compound of carbon, the product of its complete combustion. It is present in the air to the extent of 0.04 per cent. It is formed in all living cells, and in higher animals is collected by the blood and brought to the lungs and skin for excretion; it is also a product of putrefaction; it gives an acid reaction to herbivorous urine. It is found dissolved in all natural waters, and is present combined in sea shells. It is found in the blood principally combined with sodium in the serum, and is likewise combined with calcium and magnesium in the bones.

Preparation.—(1) By burning carbon or a carbon-containing substance,

$$C_6H_{12}O_6 + 12O = 6CO_2 + 6H_2O.$$
<div align="center">Sugar.</div>
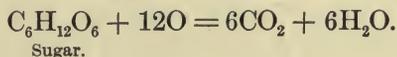
(2) By heating a carbonate,

$$CaCO_3 = CaO + CO_2.$$

(3) By the action of an acid on a carbonate,

$$Na_2CO_3 + 2HCl = 2NaCl + CO_2 + H_2O.$$

In the blood, hæmoglobin and, to a less extent, serum-albumin and primary sodium phosphate act like acids. If the gases be extracted from fresh defibrinated blood in a vacuum, all the CO_2 is removed. If sodium carbonate be added to blood, the carbonic acid belonging to this is likewise given up in a vacuum, while a simple aqueous solution of sodium carbonate is not affected. If serum be extracted *in vacuo*, only a little more than half the carbonic acid contained in it is dissociated from combination, indicating that in the previous experiment hæmoglobin had acted like an acid. If a solution of bicarbonate of sodium ($NaHCO_3$) be exhausted under the air-pump, just one-half of the CO_2 is given off, sodium carbonate (Na_2CO_3) remaining. In the serum more than one-half of the CO_2 is obtained *in vacuo*, because the serum-albumin, like the hæmoglobin, though less effectively, acts like an acid in fixing the alkali and liberating the gas. There is likewise present the action of primary phosphate on the acid carbonate,

$$NaH_2PO_4 + NaHCO_3 = Na_2HPO_4 + H_2O + CO_2.$$
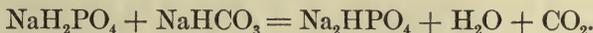
Through these agencies the tension of carbonic acid is kept high in the blood, and its escape through the walls of the alveolar capillary is not unlike the escape of gas on uncorking a bottle of carbonated water.

After drinking a carbonated water, carbonic oxide may be detected dissolved in the urine.

Properties.—A colorless, odorless gas. It is poisonous, its accumulation at first stimulating and afterwards paralyzing the nervous centres. It affects the irritability—not, however, the conducting power—of the nerves. A solution of carbonic oxide in water forms carbonic acid, H_2CO_3, and from this are derived two series of salts, primary or acid salts, $MHCO_3$, and secondary or neutral salts, M_2CO_3.

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Detection.—If expired air, or air from a bag enclosing any part of the skin, be passed through a solution of calcium or barium hydrate, a precipitate of white insoluble carbonate will be thrown down.

METABOLISM OF CARBON.—It will be remembered that there is a union of chlorine and hydrogen on exposure to sunlight. In a similar manner the chlorophyll-containing leaf of the plant, through the medium of the energy of the sun's rays, brings the molecules of water and carbonic oxide derived from the air in such a position with regard to each other that they unite to form sugar with the elimination of oxygen (reaction on p. 945). This process is called *synthesis*—the construction of a more complicated body from simpler ones. The active or "kinetic" energy from the sun required to build up the compound is stored, becoming "potential" energy in that compound, and is liberated again in exactly the same quantity on the resolution of the substance into its original constituents. So the amount of energy liberated in the decomposition of a food in the body is exactly equal to the energy needed to build it up from its excreted constituents,[1] and this liberated energy appears in the body as heat, work, and electric currents.

The plant has the power of converting sugar into starch and cellulose, and likewise into fat. Further the sugar undoubtedly unites with certain nitrogen-containing bodies, and the synthesis of proteids results. Plants containing this mixture of food-stuffs become the sustaining basis of animal life. . The animal devours these substances and either adds them to his body, or burns them to prevent destruction of his own substance : such are the objects of *food*. In contradistinction to synthesis in plants, animal life is said to be characterized by *analysis*, *i. e.*, the resolution of a complicated substance into simpler ones. This classification is not entirely accurate, many exceptions occurring on both sides ; for example, animals may convert sugar into fat, which is synthesis. The animal expires its carbon partly as carbonic acid, and partly in the form of more complex organic compounds such as urea and uric acid. Since these latter after leaving the body eventually become oxidized, and the carbon becomes completely changed to carbon dioxide, it follows that all animal carbon is finally restored to the air in the form of carbon dioxide. Thus is established the revolution of the carbon atom, made possible by the energy of the sun, between air, plants, animals, and back to air again. Burning coal, lime-kilns, volcanoes, give carbonic acid to the air. Rain water receives carbonic acid from the atmosphere, from putrefying organic matter in the soil and from the roots of trees, and ultimately much of this combines with mineral matter, or contributes to form shells in marine life.

SILICON, Si = 28.

Silicon is found in the ash of plants, and in traces in the cells and tissues of animals, being a constant constituent of hen's eggs. It appears in traces in the human urine, and in considerable quantity in herbivorous urine. It is especially present in hair and feathers. It does not seem to be of great importance to the

[1] See Rubner, *Zeitschrift für Biologie*, 1893, Bd. 30, p. 73.

life of the plant, for if corn-stalks, whose ash usually contains 20 per cent. of silica (SiO_2), be grown in a soil free from it, the plant flourishes though only 0.7 per cent. of silica is found in the ash, this having been derived from the vessel holding the soil.

Silicon Dioxide, or Silica, SiO_2.—This is the oxide of the element, and is found in quartz and sand, but not in the organism.

Silicic Acids.—The *ortho-silicic acid* (H_4SiO_4) is formed by the action of an acid on a metallic silicate,

$$Ca_2SiO_4 + 2H_2CO_3 = 2CaCO_3 + H_4SiO_4.$$

This reaction takes place in the soil, and the silicic acid so obtained is soluble in water and is a *colloid*—that is to say, is of gelatinous consistence, will not crystallize, and does not osmose through vegetable and animal membranes. However, it is in this form or in the form of soluble alkaline silicate that it is probably received by the root of the plant.[1]

Metasilicic acid has the formula H_2SiO_3, while the *polysilicic acids* ($H_2SiO_5, H_6Si_2O_7$, etc.) are numerous, and constitute the acid radicals of most mineral silicates. If silicic acid be evaporated and dried, it leaves a gritty residue of silica.

The Metallic Elements.

The metals in the body are the alkalies potassium and sodium, the alkaline earths calcium and magnesium, and the heavy metal iron.

Potassium, K = 39.

Potassium salts are found predominating in all animal cells (see p. 943), and in the milk which is manufactured from the disintegration of such cells. They are found in the blood-corpuscle to the almost complete exclusion of sodium salts. Only to a small extent do they occur in the fluids of the body and in the blood plasma ($K_2O = 0.02$ per cent. in plasma). They are excreted in the urine. Potassium salts are retained on the surface of the ground for the use of vegetation, and occur in the plant not only as inorganic but also as organic salts (tartrate, citrate, etc.).

Potassium Chloride, KCl.—Potassium chloride is a constant constituent of all animal cells and tissues, and may be absorbed with the food or be produced in the body after eating potassium carbonate or phosphate, since these salts may react with the sodium chloride. If fed, it is ordinarily balanced by its excretion, but if 0.1 gram be introduced into the jugular vein of a medium-sized dog, immediately paralysis of the heart ensues. It is a powerful poison for nerves and nervous centres. It melts when heated to a low red heat, and volatilizes at a higher heat.

Potassium Phosphates.—The primary (KH_2PO_4) and secondary (K_2HPO_4) phosphate of potassium are the principal salts of the cells of the body, and are likewise present in the urine, and to a very small extent in the blood-plasma. They are undoubtedly intimately connected with the functional activity of protoplasm. Presence of carbonic acid causes the conversion of the secondary phosphate into the primary salt, and this occurs in the blood-corpuscle as well as in the plasma :

$$K_2HPO_4 + CO_2 + H_2O = KH_2PO_4 + KHCO_3.$$
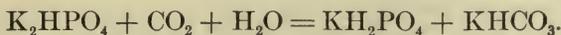
[1] Bunge: *Physiologische Chemie*, 3d ed., 1894, p. 25.

Primary acid phosphate of potassium contributes to the acid reaction of the urine, though in presence of sodium chloride there is a tendency to the formation of primary sodium phosphate and potassium chloride. It is the cause of the acid reaction in muscle in *rigor mortis* (see p. 989).

Potassium Carbonates.—The primary and secondary carbonates exist in the body only in trifling quantities. They may be produced as above described by the action of carbonic acid on the phosphates, they may be ingested with the food, or they may result in the body from the combustion of an organic salt of potassium, according to the same reaction as would take place by burning it in the laboratory,

$$K_2C_4H_4O_6 + 5O = K_2CO_3 + 3CO_2 + 2H_2O.$$
$$\text{K tartrate.}$$
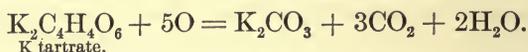
Feeding potassium carbonate or an organic salt of potassium makes the urine alkaline owing to the excretion of potassium carbonate.

Potassium salts are poisonous if introduced into the blood in too large quantities. In concentrated solutions in the stomach they produce *gastritis*, even with quickly fatal results.[1]

Zuntz believes that potassium is combined with hæmoglobin in the blood-corpuscle, and may be dissociated from it by the action of carbonic oxide.[2]

POTASSIUM IN THE BODY.—The various salts of potassium are received with the food in the manner described; the phosphate may be retained for new tissue, but the other salts are removed in the urine. They are all quite completely absorbed in the intestinal tract. In starvation, or in fever, where there is high tissue-metabolism, the body suffers greater loss of the potassium phosphate-containing tissue than it does of the sodium-rich blood, and potassium exceeds sodium in the urine (reverse of the usual proportion). Bunge[3] has noted an important influence of potassium salts. If a potassium salt be in solution together with sodium chloride, the two partially react on each other, with formation of potassium chloride. If now potassium carbonate, for example, be eaten, the same reaction occurs in the body,

$$K_2CO_3 + 2NaCl = 2KCl + Na_2CO_3.$$
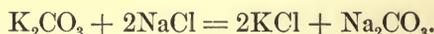
The kidney has the power of removing soluble substances which do not belong to the blood or are present in it to excess, and consequently the two salts formed as above are excreted. Hence potassium carbonate has caused a direct loss of sodium and chlorine. For this reason, if potatoes and vegetables very rich in potassium salts are eaten, sodium chloride must be added to the food to compensate for the loss. Nations living on rice do not need salt, for here the potassium content is low. Tribes living solely on meat or fish do not use salt, but care is taken that the animals slaughtered for food shall not lose the blood, rich in sodium salts, and strips of meat dipped in blood are, by some races, considered a delicacy.[4]

[1] Bunge: *Physiologische Chemie*, 3d ed., 1894, p. 136.
[2] A. Loewy und N. Zuntz: *Pflüger's Archiv*, 1894, Bd. 58, p. 522.
[3] *Op. cit.*, p. 108.   [4] Bunge, *Op. cit.*, p. 116.

Sodium, $Na = 23$.

Sodium salts belong particularly to the fluids of the body (see p. 948), blood-plasma containing 0.4 per cent. calculated to Na_2O.

Sodium chloride, $NaCl$, is found in all the fluids of the body. It is found in blood and lymph to an extent of about 0.65 per cent., in the saliva, gastric juice, milk, sweat, urine, etc. Sodium chloride, like potassium chloride, melts at a low red heat, hence the fluids of the body yield a fluid ash, with the single exception of milk, which contains a high percentage of infusible calcium phosphate. Sodium chloride is very readily soluble. In the blood it acts as a solvent on serum-globulin and other proteids, and its inert presence in proper concentration affords a medium in which the functional activity of cells and tissues is maintained. (For "physiological salt-solution" see p. 948.) From sodium chloride the hydrochloric acid of the gastric juice is prepared (see p. 952); it is also a necessary addition to every food where potassium salts are in great preponderance (see p. 964), but it is taken by most races in amounts far above these physiological necessities.

If a mixture of necessary food-stuffs—proteid, fats, starch, salts, and water—in proper proportion, but without flavor, be set before a dog, he will starve rather than touch it. A man will attempt its digestion, but the permanent support of life is impossible. A food to support life must be a well-tasting mixture of food-stuffs, for, through the action of the flavor on the mucous membrane of the mouth and stomach there is established reflexly a nervous influence causing a proper flow of the various digestive juices. Hence salt, pepper, mustard, beer, wine, and other condiments are taken with the food. What the change is, when a substance acts on the taste-buds of the tongue, for example, starting a motion such as is afterwards interpreted in the brain as flavor, is unknown. Chemical constitution gives no hint how a body will taste or smell.

In carnivora every trace of sodium chloride is absorbed by the villi from the intestinal tract. This is a proof that absorption does not depend on simple physical osmosis, in which case the intestinal contents would tend to have the same percentage composition as the blood, but upon the selective capacity of the exposed protoplasm of the villi. Sodium chloride is the principal solid constituent of sweat and of tears. Usually, however, it is lost to the body through the urine, of whose ash it forms the chief constituent. The quantity of salt in the urine is decreased during gastric digestion (see p. 952). Sodium chloride does not pass to the urine as soon as it rises above a certain quantity in the blood, but the tissues retain or give it up according to circumstances. Experiments[1] have been made on a man who ate normally 27 grams of salt daily; on reducing this to 1.4 grams the following daily excretions occurred in the urine: 9.9, 6.5, 3.8, 4.1, 3.2, 2.9, 2.9, 2.5. Then, on returning to 27 grams daily: 3.4, 7.9, 11.2, 15.8, 17.4. Experiments of abstention have never been carried so far as to produce vital disturbances, but the physiological minimum is probably very low. A dog weighing 35 kilograms may live on 0.6 gram of salt daily.[2] Sodium chloride, fed, produces of itself alone an increase

[1] Klein und Verron: *Sitzungsberichte der Wiener Academie, Mathematisch-physikalische Classe,* 1867, iv. (2), p. 622.

[2] Voit: *Hermann's Handbuch,* 1881, vi. 1, p. 367.

of water and of urea in the urine.[1] The increase of urea means increase in proteid metabolism, and is produced by all salts; it is to be explained by the increased motion of water from the cell, the same effect being seen on drinking large quantities of water (see p. 948).

Sodium sulphate, Na_2SO_4, called "Glauber's salt," is found together with potassium sulphate in the urine in the condition of preformed sulphuric acid (see p. 951). If fed, it reappears in the urine. It acts on the epithelial cells of the intestines, preventing the absorption of water, consequently causing diarrhœa. Other laxatives act in the same way.

Sodium Phosphates.—The primary (NaH_2PO_4) and the secondary (Na_2HPO_4) salts are found to a small extent in the blood-plasma and other fluids, and in the urine. As with the potassium phosphates, carbonic oxide acts when in certain excess to convert the secondary phosphate into NaH_2PO_4 and $NaHCO_3$. These two, however, may react on one another to drive off carbonic acid (see p. 961). Carnivorous urine owes its acid reaction principally to primary sodium phosphate. If a mixture of NaH_2PO_4 and Na_2HPO_4 be permitted to diffuse through membranes, the NaH_2PO_4 passes through in greater quantity, and this process may take place in the kidney.[2] Secondary sodium phosphate dissolves uric acid on warming, forming sodium acid urate and primary phosphate, which solution reacts acid (Voit). Urine standing in the cold precipitates uric acid with the formation of secondary phosphates, while the reverse reaction with return of original acidity takes place on warming the urine.

Sodium Carbonates.—Of these there are two, the primary, $NaHCO_3$, and the neutral, Na_2CO_3. The organization owes its alkaline reaction, and also its power of combining with carbonic acid, almost entirely to sodium carbonate. Saliva, pancreatic and intestinal juice are strongly alkaline with sodium carbonate, as are also blood, lymph, and other fluids. If the organization be acidified, by feeding acid to a rabbit, for example, death occurs even before complete loss of the blood's alkalinity, while venous injections of sodium carbonate at the proper time restore the animal. Carbonic oxide cannot be removed from the tissues in the acidified blood. Sodium carbonate treated with carbonic acid becomes acid sodium carbonate, and this change is effected in the internal respiration, where the cells give CO_2 to the blood. Treated with acids, both carbonates liberate carbonic oxide—a reaction which takes place in the blood (see p. 961). Bunge suggests that the acid chyme of the stomach, into whose finest particles the alkaline intestinal juice diffuses, is especially penetrable by the latter's enzymes, because liberated carbonic oxide has separated the particles of chyme from each other. The same principle would hold true of a morsel well mixed with saliva, which, as is well known, is more easily penetrable by gastric juice than one not so mixed. Sodium carbonate may be obtained for the body either directly from the food by absorption, or indirectly through

[1] Voit: *Op. cit.*, p. 160.

[2] Soubiranski: *Archiv für exper. Pathologie und Pharmakologie*, 1895, Bd. 35, p. 178.

combustion of sodium organic salts. Ingested in sufficiently large quantities, it makes the urine alkaline.

Sodium salts are undoubtedly united with serum-albumin in the plasma, forming a combination which may be dissociated by carbonic oxide.

Detection.—Sodium gives a yellow coloration to a colorless flame, and a distinctive bright line in the yellow of the spectroscope.

SODIUM IN THE BODY.—This subject has been discussed under the different salts, and likewise under potassium and hydrochloric acid; repetition here is therefore needless.

AMMONIUM, NH_4.

Ammonia, NH_3, has already been described (p. 955).

Sodium-Ammonium Phosphate, $NaNH_4HPO_4$, is an insoluble salt formed in the urine during ammoniacal fermentation.

Ammonium Carbonate, $(NH_4)_2CO_3$, is formed by the union of carbonic oxide and ammonia in the presence of water, and is therefore a usual product of putrefaction. If introduced into the blood, it is converted into urea by the liver. In *uremia* urea passes from the blood into the stomach and is there converted into ammonium carbonate, which produces vomiting through irritation of the mucous membrane. (See further discussion under Carbamic Acid and Urea.)

CALCIUM, $Ca = 40$.

Calcium is by far the most abundant metallic element in the body, and, as has been found in the dog, 99.5 per cent. belongs to the composition of the bones.[1] Outside the bones it occurs most abundantly in blood-plasma. It is found in all the cells and fluids of the body, probably loosely combined with proteid. Calcium is always accompanied by magnesium.

Calcium Chloride, $CaCl_2$, is found in small quantities in the bones.

Calcium Fluoride, CaF_2, a salt insoluble in water, is found in bone, dentine, and enamel (see p. 954).

Calcium Sulphate, $CaSO_4$, is found in small quantities in bones and rarely as part of the sediment in strongly acid urine.

Calcium Phosphates.—Of these there are three—primary, $CaH_4(PO_4)_2$, secondary, $CaHPO_4$, and tertiary, $Ca_3(PO_4)_2$. The tertiary phosphate is insoluble in water, the secondary only very slightly soluble, but the primary salt is soluble. The tertiary and secondary phosphates are insoluble in alkali, but soluble in mineral acids and in acetic acid. The tertiary phosphate forms the largest mineral constituent of the bones (83.89 per cent., Zalesky) and of dentine and enamel. Tertiary phosphate of calcium likewise occurs in the blood; how it is held in solution it is difficult to say, though it is probably loosely combined with proteid. In a similar way it is combined with the protoplasm of the cell. It is largely found in the ash of milk, having been in previous chemical combination with casein. Tertiary phosphate of calcium is continuously excreted into the intestinal tract. It is present in the acid gastric juice, but only in traces in the alkaline saliva, pancreatic juice, and in the nearly

[1] Heiss: *Zeitschrift für Biologie*, 1876, Bd. 12, p. 165.

neutral bile. Tertiary phosphates never occur in the urine, except as a sediment after the urine has attained an alkaline reaction, being formed from the acid phosphates. In carnivorous urine the calcium present occurs as primary and secondary phosphate, the solution of the latter being aided by the primary alkali phosphate and sodium chloride. Occasionally a coat is noticed on the surface of the urine, an appearance once thought to be a sign of pregnancy. This coat is now known to consist chiefly of secondary phosphate of calcium, which may crystallize out on the urine becoming alkaline. Calcium does not occur as phosphate in an alkaline urine (see p. 959).

Calcium Carbonates.—Of these there are two, the primary or acid, $CaH_2(CO_3)_2$, and the secondary or neutral carbonate, $CaCO_3$. Neutral calcium carbonate is the substance of which sea shells, coral, egg-shell, and otoliths consist. It is found in the ash of bones to the extent of 13.032 per cent. (Zalesky). Apatite is a mineral having the formula $Ca_{10}F_2(PO_4)_6$, and Hoppe-Seyler, using Zalesky's figures, believes that bone has a composition represented by $Ca_{10}CO_3(PO_4)_6$, or $3Ca_3(PO_4)_2,CaCO_3$, in which CO_3 has the position of F_2 in apatite. In the wasting of the mineral matter of bones in *osteomalacia* this formula of composition remains constant,[1] one molecule of calcium carbonate always being removed for every three molecules of the phosphate. Neutral calcium carbonate is insoluble in water or alkali, but dissolves in water containing carbonic oxide to form the soluble acid carbonate, $CaH_2(CO_3)_2$. This is found in blood and lymph, and in minute quantities in all the tissues. It is found in herbivorous urine, which contains carbonic acid in excess, but it is soon deposited as neutral carbonate as the carbonic oxide diffuses into the air. It occurs in all alkaline and neutral urines, though to a less extent than calcium phosphate in acid urines. It is found in pancreatic juice and in the saliva, from which latter is derived the calcic carbonate which, mixed with bacteria and other organic matter, is deposited as *tartar* on the teeth.

The ferment rennet does not act in the absence of calcium salts. The coagulation of the blood requires the presence of calcium salts,[2] and fibrin always contains calcium. If ten parts of blood be drawn into one part of a 1 per cent. solution of potassium oxalate, thus precipitating the calcium, no coagulation takes place, but on the addition of calcium chloride a typical fibrin forms. A solution of sodium oxalate passed through a beating excised heart causes it to cease beating[3] and nerves and muscles lose their irritability when calcium salts are abstracted from them with sodium oxalate.[4] These facts illustrate the intimate relation between calcium salts and the functional activity of protoplasm.

Detection.—Ammonium oxalate in neutral or alkaline solutions of calcium salts gives a precipitate of calcium oxalate—a white powder, insoluble in acetic or oxalic acid.

[1] M. Levey: *Zeitschrift für physiologische Chemie,* 1894, Bd. 19, p. 239.
[2] Arthus et Paget: *Archives de Physiologie,* vlo. ii. p. 739.
[3] Howell and Cooke: *Journal of Physiology,* 1893, vol. 14, p. 219, note.
[4] Howell: *Journal of Physiology,* 1894, vol. 16, p. 476.

CALCIUM IN THE BODY.—Calcium salts are especially needed in childhood for the growth of the bones. It has been estimated that the human suckling requires 0.32 gram CaO daily, and in the milk for that time is contained 0.55 gram to 2.37 grams, so that there may easily be lack of CaO when absorption is unfavorable. In children with rickets the bones contain too little calcium, and are abnormally weak and flexible. This same condition may be reproduced in young growing dogs by feeding them entirely on meat and fat, which contain too little calcium for proper skeletal development.[1] Such dogs grow rapidly in size, especially around the thorax, while the pelvis remains ludicrously small, the extremities become bent and finally incapable of supporting the weight of the body. A puppy of the same litter fed on the same food but with the addition of bones grows normally. In certain cases even when children are fed with sufficient calcium they still have the rickets. This might be due to a lack of ability to absorb the salts, but this Rüdel[2] has disproved. To a child having rickets he administered a calcium salt, and confirmed its absorption by the increase in the calcium contents of the urine, the result being the same as with a normal child. (Example: Normal day, 0.0196 gram CaO in urine; after feeding 1.4 grams CaO dissolved in acetic acid the amount in the urine rises to 0.0396 gram for the twenty-four hours.) Rüdel therefore concludes that the cause of rickets may be in a local change of the bones themselves, whereby calcium salts are not deposited in the normal manner.

In *osteomalacia* there occurs a solution of the salts of the bones in adult life, called softening of the bones. In *osteoporosis*, which is a simple atrophy of the bones, similar effects are produced. Voit[3] fed a pigeon for a year on washed wheat and distilled water, at the end of which time the pigeon apparently did not differ from the normal bird. A few months later a wing was broken, and the autopsy discovered osteoporosis in high degree, the skull being especially attacked. Weiske[4] has shown that rabbits ultimately die when fed on oats which are poor in calcium; the oats yield an acid ash and produce an acid urine. On autopsy osteoporosis is found. This does not take place when calcium carbonate is added to the food. Whether the loss of salts to the bone is due to a normal metabolism, or to solution due to the production of acids in the metabolism of proteid, is an unanswered problem (see pp. 950, 955) the discussion of which lack of space forbids.[5] In such experiments as the above, the percentage of ash is always diminished, while the percentage of organic matter always rises, whereas the actual percentage composition of the ash itself remains the same. This is a strong argument in favor of the view that bone is a mineral of definite chemical composition. The mineral matter of bone is believed by some to be loosely combined with the organic material, principally ossein, but of this there is no proof.

The exact amount of calcium salt necessary to keep up the supply in the adult body is unknown, but it must be exceedingly small. A dog of 3.8 kilograms eating with his food 0.043 gram CaO maintains his calcium equilibrium (Heiss).

Regarding the absorption of calcium salts, it has long been questioned whether inorganic salts can be absorbed, since, it was argued, insoluble phosphate would immediately be precipitated in the blood. It has, however, been conclusively shown that such salts when eaten produce an increase in the calcium of the urine[6] and it is known that blood has a special capability for carrying calcium phosphate. Calcium carbonate and chloride are capable of

[1] E. Voit: *Zeitschrift für Biologie*, 1880, Bd. 16, p. 70.

[2] *Archiv für exper. Pathologie und Pharmakologie*, 1893, Bd. 33, p. 90.

[3] *Hermann's Handbuch*, 1881, vi. 1, p. 379.

[4] *Zeitschrift für Biologie*, 1894, Bd. 31, p. 421.

[5] See Weiske, *loc. cit.*; Bunge, *Physiologische Chemie*, 3d ed., 1894, p. 104; V. Noorden, *Pathologie der Stoffwechsels*, 1893, pp. 48 and 413.   [6] Rüdel, *Op. cit.*, p. 79.

absorption, while absorption of the phosphate may be considered as still in doubt. If calcium chloride be given, a little of the calcium appears in the urine, and all of the chlorine, this being due to the conversion in the intestine of calcium chloride into calcium carbonate and sodium chloride, which latter is completely absorbed. Organic salts of calcium such as the acetate are absorbable, as are probably proteid combinations with calcium such as casein. Milk and egg-yolk are the foods richest in calcium salts, cow's milk containing more calcium to the liter than does lime-water.[1]

The excretion of calcium takes place in major part as triple phosphate from the wall of the intestine, in minor part through the urine (for the latter see pp. 959 and 968). It is excreted during starvation, and is the principal constituent of starvation feces (Voit). The secretions of the intestines, according to Fr. Müller,[2] hardly contain enough calcium to account for that found in the feces, so that it is probably excreted by the epithelial cells of the villus. In starvation the source of excreted calcium is principally from the breaking down of tissue, but partially from the metabolism of the bones. The excretion is never large. On subcutaneous injection of small amounts of calcium acetate in dogs,[3] the calcium excretion may be raised for several days. On venous injection of 0.8 gram CaO as acetate, after one hour but 0.3 gram could be found above the normal in the blood, and analysis of the liver, kidney, spleen, and intestinal wall failed to reveal more than the usual minimal amounts of calcium. As it is never rapidly excreted it must have been temporarily deposited in some unknown part of the body. Rey[4] believes the large intestine to be the principal organ of calcium-excretion, while F. Voit[5] attributes this function to the small intestine.

Strontium, $Sr = 87.5$.

Cremer[6] has shown, on adding strontium phosphate to almost calcium-free food of young growing dogs, that the strontium line could be detected in the subsequent spectral analysis of their bones. Weiske,[7] on feeding young rabbits with food nearly free from calcium, and with addition of strontium carbonate, found the ash in some of the bones to contain, in the place of CaO, as high as 4.09 per cent. of SrO. In both of the above experiments the skeleton remained very undeveloped in comparison with the normal, so that strontium cannot be considered a physiological substitute for calcium.

Magnesium, $Mg = 24.3$.

This is the second in importance of the alkaline earths. It is present wherever calcium is found, but in comparison with calcium it has been little investigated. It occurs principally as phosphate, but is found as carbonate in herbivorous urine. Of the total quantity of magnesium in the dog, Heiss

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[1] Bunge: *Physiologische Chemie*, 3d ed., 1894, p. 101.

[2] *Zeitschrift für Biologie*, 1894, Bd. 20, p. 356.

[3] Rey: *Archiv für exper. Pathologie und Pharmokologie*, 1895, Bd. 35, p. 298.

[4] Rey, *loc. cit.*　　　　　　　　　　[5] *Zeitschrift für Biologie*, 1893, Bd. 29, p. 325.

[6] *Sitzungsberichte der Gesellschaft für Morphologie und Physiologie in München*, 1891, Bd. 7, p. 124.

[7] *Zeitschrift für Biologie*, 1894, Bd. 31, p. 437.

found that 71 per cent. belonged to the bones. It is found decidedly predominating over calcium in muscle, but is less in quantity than calcium in the blood.

Magnesium Phosphates.—Magnesium tertiary phosphate, $Mg_2(PO_4)_3$, is found in the ash of bones to the extent of about 1 per cent., is present in blood and especially in muscle, probably in combination with proteid, and contributes to the functional activity of protoplasm. It is continuously excreted by the walls of the intestinal canal. The primary and secondary phosphates of magnesium are found in carnivorous urine, solution of the latter being aided by the presence of primary alkali phosphate and sodium chloride. Tertiary phosphate of magnesium is insoluble in water, the secondary very slightly so, the primary quite soluble; but all are soluble in acids. In the ammoniacal fermentation of the urine, *ammonium magnesium phosphate*, $MgNH_4$-PO_4, is precipitated as a fine crystalline powder insoluble in alkalies. Whenever this fermentation takes placed, whether in the bladder or, by similar reaction, in the intestines (herbivora especially), stones are formed.

Magnesium Carbonates.—The neutral carbonate, $MgCO_3$, is insoluble in water, but soluble in water containing carbonic oxide, forming secondary or acid carbonate, $MgH_2(CO_3)_2$. This latter occurs in herbivorous urine.

Detection.—A mixture of sodium phosphate and ammonia containing an ammonium salt (NH_4Cl) precipitates from magnesium solutions magnesium ammonium phosphate.

Magnesium in the Body.—Considerations regarding the absorption of calcium apply likewise to magnesium. It is absorbed by the intestine as inorganic and probably as organic combinations. If growing rabbits be fed on a diet poor in calcium salts, but containing magnesium carbonate, the bones may be brought to contain double the normal quantity of magnesium, but the skeletal development remains far behind that of a normal rabbit, and therefore magnesium can in no sense be considered a substitute for calcium.[1] The magnesium salts, whether phosphate or carbonate, being more soluble than the calcium salts, occur in the urine in greater abundance. Indeed, in carnivorous urine the major part of excreted magnesium is found in the urine, the balance being given off through the intestinal wall to the feces. In starvation the source of the excreted magnesium is from the bones, and especially from destruction of its combination in proteid metabolism.

<div align="center">Iron, $Fe = 56$.</div>

This is the one heavy metal which is an absolute necessity for the organism. About three grams occurs in the average man. It has been demonstrated of certain bacteria that they will not develop in the absence of iron, and this is believed to be true of all protoplasm. Iron is found throughout the body, and is especially an ingredient of hæmoglobin (0.4 per cent.), which carries oxygen to the tissues. It is found deposited in the liver and the spleen as ferratin, hepatin, and other less investigated organic compounds.

[1] Weiske : *Zeitschrift für Biologie*, 1894, Bd. 31, p. 437.

It is found in muscle washed free from blood. Iron appears in urine and in milk as organic compounds, and in the bile, gastric juice, and intestines as phosphate, in the feces as sulphide. Iron occurs in two forms, the ferro- and ferri- compounds, in which it has respectively two and three bonds.

Ferrosulphide, FeS.—This is found in the feces and is the product of the action of sulphuretted hydrogen or alkaline sulphide on both inorganic iron and likewise, more slowly, on organic iron-containing compounds (ferratin, hæmatogen, etc.). Ammonium sulphide acts in a similar manner, and, in all cases, ferric salts are reduced to ferrous:

$$2FeCl_3 + 3(NH_4)_2S = 2FeS + 6NH_4Cl + S.$$
Ferric chloride.
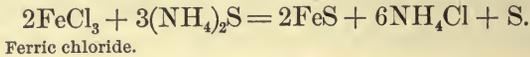
Ferric Phosphate, $FePO_4$.—This is found in the gastric juice, bile, and probably in the intestinal juice;[1] it is not, as many have believed, given off by the epithelia of the intestines. It is soluble in mineral acids, but insoluble in water, alkalies, or acetic acid.

Detection.—Ammonium sulphide gives a black precipitate of ferrous sulphide in all iron solutions. Ferrocyanide of potassium gives a deep blue coloration (Berlin-blue) to solutions of ferric salt. Ferricyanide of potassium gives Turnbull's blue, very similar to Berlin-blue, with solutions of ferrous salts.

IRON IN THE BODY.—The amount of iron in the urine is very small, amounting daily in a large starving dog to 0.0013–0.0049 gram.[2] Feeding iron compounds does not increase the amount of iron in the urine. Forster[3] fed a dog of 26 kilograms for thirty-eight days with washed meat containing 0.93 grams of iron, and in the feces were found 3.59 grams belonging to the same period. Here there was a loss of 2.66 grams[4] of iron from the body, and the necessity of iron as a food was established.

Concerning the method and the amount of iron-absorption, considerable difficulty has been encountered owing to the fact that both absorptive and secretive organs lie in the intestinal canal. On feeding a dog for thirteen days with meat containing 0.180 gram Fe, there were found in urine and feces for the same time 0.1765 gram Fe; then to the same food for a similar length of time were added 0.441 gram Fe (as sulphate), making in all 0.636 gram Fe, and of this 0.6084 gram were recovered in the excreta.[5] This experiment proves only that such absorption as may take place is pretty nearly balanced by the excretion. After eating blood the feces are found to contain much hæmatin, and it is believed that iron cannot be absorbed in that way. Bunge[6] has sought for one of the antecedents of hæmoglobin in egg-yolk, and has described it as an iron-containing nucleo-albumin, which he names hæmatogen. That and similar nucleo-albumins existing in plants he conceives to be the source of absorbable iron, while inorganic salts of iron aid only indirectly by forming iron sulphide, thus preventing the same formation from organic iron (see above). Marfori[7] has prepared a substance from proteid and iron salts, called ferratin, which contains 4 to 8 per cent. of iron; it is a compound unaffected by gastric juice or by boiling; it

[1] Macallum: *Journal of Physiology*, 1894, vol. 15, p. 268.

[2] Forster: *Zeitschrift für Biologie*, 1873, Bd. 9, p. 297.   [3] *Loc. cit.*

[4] This figure is probably too high, but the principle itself is fundamental. See Voit, *Hermann's Handbook*, 1881, vi. 1, p. 385.

[5] Hamburger: *Zeitschrift für physiologische Chemie*, 1878, Bd. 2, p. 191.

[6] *Zeitschrift für physiologische Chemie*, 1884, Bd. 9, p. 49.

[7] *Archiv für exper. Pathologie und Pharmakologie*, 1891, Bd. 29, p. 212.

is soluble in the alkaline intestine, where it is but slowly affected by alkaline sulphide. Now this same ferratin is found in the body itself, especially in the liver,[1] although not the only iron-containing substance of the liver.[2] If ferratin be fed, the quantity of it increases in the liver. If a dog be fed on milk, which is always poor in iron, and he be bled from time to time, the ferratin disappears from the liver, being used for the formation of new red blood-corpuscles.[3] Such a liver does not change color when placed in dilute ammonium sulphide, while one containing ferratin or other iron compounds gradually turns black from iron sulphide. As it is not decomposed by boiling, ferratin is found in the usual cooked meat. Concerning the influence of inorganic salts, Schmiedeberg agrees with Bunge that the formation of iron sulphide protects the ferratin from attack.

The insolubility of iron salts in alkaline solutions has raised the question of their absorption by the blood. If inorganic iron salts be injected into a vein, the iron reappears chiefly in the intestines, with only 3 to 4 per cent. in the urine (Jakobj): in too great quantities they have powerful toxic properties. Gottlieb[4] administered 0.1 gram of iron as sodium iron tartrate subcutaneously to a dog during a period of nine days; twenty-eight days after the first injection 0.0969 gram Fe had been removed in the excreta over and above the normal excretion calculated for the same time. It was shown that this iron was especially stored in the liver. It may be argued that such iron, being foreign to the organization, was deposited in the liver and gradually excreted through the bile, as other heavy metals, mercury, copper, lead, would be. Kunkel[5] fed mice and to the food of half their number added a solution of oxychloride of iron ($FeCl_3, 4Fe(OH)_3$, liquor ferri oxychlorati): in the livers of those fed with iron, iron was present to a greater extent than in the others; but here, again, the surplus can be attributed to the sulphide-forming protective power of the added salts, which Kunkel admits, though maintaining the contrary ground. The only proof of the absorption of inorganic salts emanates from Macallum,[6] who showed, after feeding chloride, phosphate, and sulphate to guinea-pigs, that the epithelial cells and the subepithelial leucocytes of the intestines gave a strong microchemical reaction for iron with ammonium sulphide. With small doses this was observed only near the pylorus, for iron is soon precipitated by the alkali of the intestines, but where the iron salt was in sufficient quantity to neutralize the intestinal alkali it could be absorbed the whole length of the small intestines. Whether inorganic iron unites with proteid before absorption or not is unknown.

Regarding the transformation of iron compounds after absorption into hæmoglobin, little is known except that the necessary synthesis takes place in the spleen, in the bone-marrow, and probably in the liver. On the destruction of red blood-corpuscles, proteid bodies holding iron in combination are deposited in the cells of the liver and spleen, this being noticeable in pernicious anæmia. On the production of icterus with arseniuretted hydrogen, similar iron compounds are noted in the liver, being cleavage products of hæmoglobin in its transformation to biliary coloring matter. The amount of iron normally excreted from the body is far less than the corresponding biliary coloring matter (see Hæmochromogen), showing that the rest of the iron is retained for further use in constructing new hæmoglobin.

Iron is excreted as phosphate in the gastric juice, in bile (in considerable quantity), and, according to Macallum,[7] in the intestinal juice. In the urine it is present as an unknown organic compound.

A newborn child or animal has, proportionately to its weight, far more iron than at any

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[1] Marfori, *loc. cit.*, and Schmiedeberg, *Archiv für exper. Pathologie und Pharmakologie*, 1894, Bd. 33, p. 101.

[2] Vay: *Zeitschrift für physiologische Chemie*, 1895, Bd. 20, p. 398.

[3] Schmiedeberg, *Op. cit.*, p. 110.

[4] *Zeitschrift für physiologische Chemie*, 1891, Bd. 15, p. 371.

[5] *Pflüger's Archiv*, 1891, Bd. 50, p. 11.   [6] *Journal of Physiology*, 1894, vol. 16, p. 268.

[7] *Op. cit.*, p. 278.

other time of its life. This iron is lost only very slowly, hence the very small quantity of iron in the milk answers all necessities. The other salts of the milk are in the same proportion to one another as are the salts in the newborn animal.

Tables representing generally accepted analyses of the mineral constituents of the more important fluids and cells of the body are subjoined. Only very pronounced differences are to be taken into consideration in drawing conclusions, for analyses of animals of different species, or of the same species, or even of the same animal at different times, show wide variations. The tables represent parts in 1000 of fresh substance:

I.

	K_2SO_4.	KCl.	NaCl.	Na_2CO_3.	$CaCO_3$.	Ca_3PO_4.	$MgCO_3$.	$Mg_3(PO_4)_2$.	$FePO_4$.
Saliva[1] (dog)	0.209	0.940	1.546	0.940	0.150	0.113			
Pancreas[2] (dog) . .	. . .	0.93	2.53	3.30(Na_2O)	. . . .	0.07	0.01(MgO)	0.01	
Gastric juice[3] (dog).	. . .	1.125	2.507	. . . .	0.624(CaO_2)	1.729	. . . .	0.226	0.082
Fresh bile[4] (dog) . .	0.022	. .	0.185	0.056	0.030	0.039	0.007(MgO)	. . . .	0.021

II.

	K_2O.	Na_2O.	CaO.	MgO.	Fe_2O_3,	Cl.	P_2O_5.
Blood-serum[5] (dog)	0.202	4.341	0.176	0.041	0.01	3.961	0.489
Blood-corpuscles[6] (pig)	5.543	0	0	0.158	. . .	1.504	2.067
Blood-serum[6] (pig)	0.273	4.272	0.136	0.038	. . .	3.611	0.188
Muscle[7] (ox)	4.654	0.770	0.086	0.412	0.057.	0.672	4.644
Milk[8] (cow).	1.67	1.05	1.51	0.20	0.003	1.86	1.60

THE CHEMISTRY OF THE COMPOUNDS OF CARBON.

DERIVATIVES OF METHANE.

The complicated structure and the great variety of the compounds of carbon are due to the fact that carbon-atoms have a greater power for union with one another than have the atoms of other elements.

Saturated Hydrocarbons or Paraffins (formula, C_nH_{2n+2}).—

Methane, CH_4, gas.
Ethane, C_2H_6, "
Propane, C_3H_8, "
Butane, C_4H_{10}, "

Pentane, C_5H_{12}, liquid at 38°.
Hexane, C_6H_{14}, " 71°.
Heptane, C_7H_{16}, " 98°.
etc.

These are the constituents of petroleum and natural gas, and are formed by the action of low heat on coal under pressure in the absence of oxygen, and are probably derived from fossil animal fat, since it has been shown that the paraffins may be obtained in large

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[1] Herter: Hoppe-Seyler's *Physiologische Chemie*, p. 192.
[2] Kröger: Quoted by Halliburton, *Chemistry, Physiological and Pathological*, p. 656.
[3] Bidder and Schmidt: Quoted by Halliburton, *Op. cit.*, p. 638.
[4] Hoppe-Seyler: *Physiologische Chemie*, p. 302.
[5] Bunge: *Ibid.*, 3d ed., p. 265.
[6] *Op. cit.*, p. 222 (Bunge finds Na_2O exceeds K_2O in the blood-corpuscles of cattle).
[7] Bunge: *Zeitschrift für physiologische Chemie*, 1885, Bd. 9, p. 60.
[8] Bunge: *Physiologische Chemie*, 3d ed., p. 100.

quantity by heating fish oil at a pressure of ten atmospheres.[1] The paraffins may all be formed synthetically from methane by the action of sodium on halogen compounds of the group:

$$2CH_3I + 2Na = C_2H_6 + 2NaI.$$
$$C_2H_5I + CH_3I + 2Na = C_3H_8 + 2NaI.$$
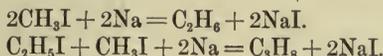
This may be continued to form a theoretically endless number of compounds. Paraffins are notably resistant to chemical reagents, not being affected by either concentrated nitric or sulphuric acids. *Vaseline* contains a mixture of paraffins melting between 30° and 40°. By *massage* vaseline may be absorbed by the skin, through the epithelial cells of the sebaceous glands. In rabbits and dogs, directly after such treatment, it may be detected deposited especially in muscle, but it is for the greater part destroyed in the body.[2]

MONATOMIC ALCOHOL RADICALS.

These are radicals which may be considered as paraffins less one atom of hydrogen, and therefore having one free bond. They form the basis of homologous series of alcohols and acids.

Monatomic Alcohols (general formula, $C_nH_{2n+1}OH$).—

Methyl alcohol, CH_3OH.	Amyl alcohol, $C_5H_{11}OH$.
Ethyl alcohol, C_2H_5OH.	Hexyl alcohol, $C_6H_{13}OH$.
Propyl alcohol, C_3H_7OH.	Heptyl alcohol, $C_7H_{15}OH$.
Butyl alcohol, C_4H_9OH.	etc.

General Reactions for Primary Alcohols.—(1) Alcohols treated with sulphuric acid give ethers (see Ethyl ether):

$$2CH_3OH + H_2SO_4 = \frac{CH_3}{CH_3}{>}O + H_2O + H_2SO_4.$$

Methyl ether.
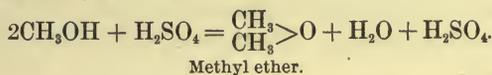
(2) Alcohols oxidized give first aldehyde and then acid:

$$CH_3OH + O = HC{<}^O_H + H_2O.$$

Methyl aldehyde.

$$CH_2O + O = HC{<}^O_{OH}$$
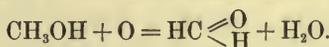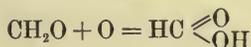
Formic acid.

(3) Primary alcohols may be prepared[3] by reduction of the aldehyde with nascent hydrogen,

$$CH_3CHO + H_2 = CH_3CH_2OH$$

Ethyl aldehyde.   Ethyl alcohol.
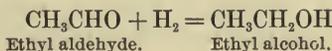
and similarly by reduction of the acid.

Secondary Alcohols.—From propyl alcohol upward there are alcohols isomeric with the primary alcohols, but in which the grouping $R—CHOH—R$ is characteristic. These are secondary alcohols, and may be produced by the action of nascent hydrogen on ketones:

$$CH_3 \text{-} CO \text{-} CH_3 + H_2 = CH_3 \text{-} CHOH \text{-} CH_3.$$

Acetone.   Isopropyl alcohol.
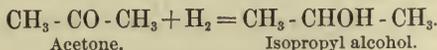
Tertiary Alcohols.—These have the general formula $R_3{=}COH$.

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[1] Engler: *Berichte der deutschen chemischen Gesellschaft*, 1888, Bd. 21, p. 1816.

[2] Soubiranski: *Archiv für exper. Pathologie und Pharmakologie*, 1893, Bd. 31, p. 329.

[3] Again attention is called to the fact that the list of these reactions is in no wise complete, but only intended to be suggestive of what should be mastered from a text-book on general chemistry.

Monobasic Acids—The Fatty Acids (formula, $C_nH_{2n}O_2$).—

Formic acid, $H\ COOH$.
Acetic acid, CH_3COOH.
Propionic acid, C_2H_5COOH.
Butyric acid, C_3H_7COOH.
Valerianic acid, C_4H_9COOH.
Caproic acid, $C_5H_{11}COOH$.
Œnanthylic acid, $C_6H_{13}COOH$.
Caprylic acid, $C_7H_{15}COOH$.

Capric acid, $C_9H_{19}COOH$.
Lauric acid, $C_{11}H_{23}COOH$.
Myristic acid, $C_{13}H_{27}COOH$.
Palmitic acid, $C_{15}H_{31}COOH$.
Stearic acid, $C_{17}H_{35}COOH$.
Arachidic acid, $C_{19}H_{39}COOH$.
Cerotic acid, $C_{26}H_{53}COOH$.
Melissic acid, $C_{29}H_{59}COOH$.

These are organic compounds of acid reaction in which one atom of hydrogen is replaceable by a metal or an organic radical. Combined with glycerin the higher members of the series (from C_4 up) form the neutral fats of the organization. By distillation of a fatty acid with alkaline hydrate, a hydrocarbon is obtained containing one carbon atom less than the acid used.

$$CH_3COONa + NaOH = CH_4 + Na_2CO_3.$$
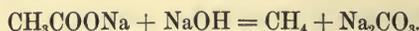
Preparation.—(*a*) Through oxidation of alcohols or of aldehydes,

$$C_2H_5OH + O_2 = CH_3COOH + H_2O.$$
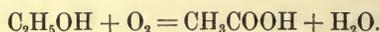
(*b*) Through the action of carbon dioxide on the sodium compound of alcohol radicals,

$$CH_3Na + CO_2 = CH_3COONa.$$
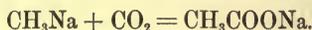
Compounds of Methyl.

Methane, or Marsh-gas, CH_4.—This gas is produced by intestinal putrefaction, and is the only hydrocarbon found in the body. It is formed in largest quantities from the fermentation of cellulose, which takes place, according to Hoppe-Seyler, thus:

$$C_6H_{10}O_5 + H_2O = C_6H_{12}O_6.$$

$$C_6H_{12}O_6 = 3CH_4 + 3CO_2.$$
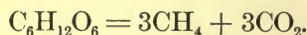
Tappeiner[1] finds that less CH_4 than CO_2 is produced in cellulose fermentation in the intestine, and that the lower fatty acids (acetic to valerianic) are also formed. This putrefaction is especially great in the *cæcum* of herbivora. Methane is also a product of putrefaction of proteid (but not of casein, since it is not present when milk is fed). Through the putrefaction of cholin, a decomposition product of lecithin, methane is likewise evolved in small quantity.[2] Further, methane may be produced from the putrefaction of metallic acetates:

$$CaC_4H_6O_4 + 2H_2O = CaCO_3 + CO_2 + H_2O + 2CH_4.$$

Properties.—A colorless, odorless gas which burns with a dull flame. It is absorbed by the blood, and in the herbivora is given off by the lungs often in larger quantity than from the rectum.[3] In man only little is produced. Methane is not oxidized in the body, and is harmless when respired, even when 10 or 20 per cent. in volume is present.[4]

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[1] *Zeitschrift für Biologie*, 1884, Bd. 20, p. 84.

[2] Hasebroek: *Zeitschrift für physiologische Chemie*, 1888, Bd. 12, p. 148.

[3] B. Tacke: Quoted by Bunge, *Physiologische Chemie*, 3d ed., 1894, p. 284.

[4] Paul Bert: *Comptes rendus de la Société de Biologie*, 1885, p. 523. Abstract in **Maly's** *Jahresbericht über Thierchemie*, 1886, Bd. 16, p. 364.

Trichlormethane, or Chloroform, $CHCl_3$.—This temporarily paralyzes nerves and nerve centres. It is principally removed as vapor through the lungs, but is partially burned, thereby increasing the inorganic chlorides in the urine.[1] After giving chloroform it may itself occur in the urine, and likewise a substance which reduces Fehling's solution, glycuronic acid (which see).

Methyl Aldehyde, or Formic Aldehyde, $H.CHO$.—This may be produced synthetically by passing vapor of methyl alcohol mixed with air over an ignited platinum spiral,

$$CH_3OH + O = H.CHO + H_2O.$$
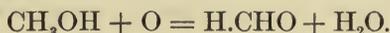
On cooling the vapor, the aldehyde is found dissolved in the alcohol. On evaporation of the alcohol, the aldehyde, through condensation of three of its molecules, forms a crystalline body having the composition $(HCHO)_3$ and called paraformic aldehyde. This latter treated with calcium or magnesium hydrate again suffers condensation with the production of *formose*, $C_6H_{12}O_6$, a sweet-tasting sugar (Butlerow, Loew) identical with *i*-fructose (Fischer). Baeyer[2] first suggested that the sugar synthesis in the plant was analogous to the above process. He conceived the reduction of carbon dioxide to carbon monoxide, which united with chlorophyll, and afterward through hydrogen addition became formic aldehyde; then in upward stages became metaformic aldehyde, sugar, starch, and cellulose. Reinke[3] has shown the presence of formic aldehyde in chlorophyll leaves, and believes its production due to the reduction of carbonic acid through the power of the sun on the leaf, thus:

$$H_2CO_3 = HCHO + O_2.$$

Bach[4] states that carbonic acid and water in the presence of uranium acetate yield formic aldehyde and nascent oxygen when placed in the sun. According to Stocklasa,[5] 400 grams of fresh leaves (128 grams dry) of the sugar beet form synthetically and send to the beet root 31 grams of cane-sugar in thirty days.

General Behavior of Aldehydes.—They act as reducing agents, being readily oxidized to the corresponding acid. With nascent hydrogen they are reduced to alcohols. A distinctive reaction of aldehydes and ketones is their union with phenyl hydrazin, C_6H_5—NH—NH_2, giving *hydrazones*:

$$CH_3CHO + C_6H_5NHNH_2 = CH_3.CH:N.NH.C_6H_5 + H_2O.$$
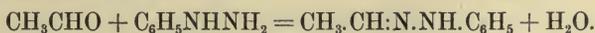
Preparation.—By distillation of the salt of an acid with a salt of formic acid:

$$CH_3COONa + HCOONa = Na_2CO_3 + CH_3CHO.$$
$$\text{Aceto-aldehyde.}$$
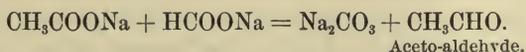
Methyl Mercaptan, CH_3SH.—This is a product of bacterial action on proteid,[6] and is found with H_2S in the intestine. It is, furthermore,

[1] A. Zeller: *Zeitschrift für physiologische Chemie*, 1883, Bd. 8, p. 74.

[2] *Berichte der deutschen chemischen Gesellschaft*, 1870, Bd. 3, p. 67.

[3] *Ibid.*, 1881, Bd. 14, p. 2144.

[4] *Ibid.*, 1894, Bd. 26, pp. 502 and 689.

[5] Stocklasa: *Zeitschrift für physiologische Chemie*, 1895, Bd. 21, p. 83.

[6] M. Nencki: *Archiv für exper. Pathologie und Pharmakologie*, 1891, Bd. 28, p. 206.

given off on fusing proteid with potash.[1] Methyl mercaptan boils at 5°, and has a strong odor. It is found in the urine, especially after eating asparagus, giving to it a peculiar smell.[2] According to Rubner[3] the smell of cooked cabbage, cauliflower, and the like, is due to methyl mercaptan.

Methyl Telluride, $(CH_3)_2Te$.—A gas of penetrating odor found in all excreta of an animal after feeding salts of telluric, H_2TeO_4, or tellurious, H_2TeO_3, acid. The salt is reduced to metallic tellurium in the body, which unites with a methyl group in some way liberated in the cells.[4] Metallic tellurium may be microscopically seen deposited in various cells, and the odor of $(CH_3)_2Te$ may be detected for months after the last dose has been given to a dog.[5]

Methyl Selenide, $(CH_3)_2Se$.—This is very similar to the last-named substance, but more poisonous.

Formic Acid, HCOOH.—Found in ants, and obtained by distilling them with water. Present likewise in stinging-nettles and in the sting of honey-bees, wasps, and hornets. Its salts are found in minute quantities in normal urine, and are present especially in both blood and urine in such diseases as include an abnormal proteid decomposition—such as leucocythæmia, fever, diabetes.[6] Formic acid may be obtained from the oxidation of methyl alcohol, of sugar, and of starch, but not from the latter two in the body. Likewise by heating oxalic acid,

$$\begin{matrix} COOH \\ | \\ COOH \end{matrix} = HCOOH + CO_2.$$

It is found in the urine after feeding methyl alcohol and other methyl derivatives, such as oxymethyl-sulfonic acid, or formic aldehyde. Ethyl alcohol, on the contrary, does not yield it.[7] It is the lowest member of the fatty-acid series, the most volatile, and the least readily oxidized in the body. If formates be fed they appear readily in the urine. It has a penetrating odor, acts as a reducing agent ($HCOOH + O = CO_2 + H_2O$), and therefore precipitates Fehling's solution. Outside of the body it readily undergoes oxidation to water and carbonic acid. It produces inflammation of the skin. A 7 per cent. solution given to a rabbit *per os* has a most powerful corrosive action and results fatally, formic acid being found in the urine.

Ethyl Compounds.

Ethyl Hydroxide, or **Ethyl Alcohol,** C_2H_5OH.—This has been detected in minute quantity in the normal muscle of rabbits, horses, and cattle.[8] It is formed by the fermentation of dextrose, the process taking place in the yeast-cell itself, alcohol and carbonic acid being the chief excretory products; like-wise, to a very small extent, the higher alcohols, propyl, isobutyl, amyl, the

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[1] M. Rubner: *Archiv für Hygiene,* 1893. [2] Nencki, *loc. cit.* [3] *Loc. cit.*

[4] Hofmeister: *Archiv für exper. Pathologie und Pharmakologie,* 1894, Bd. 33, p. 198.

[5] Beyer: *Archiv für Physiologie,* Jahrgang 1895, p. 225.

[6] See R. Jaksch: *Zeitschrift für physiologische Chemie,* 1886, Bd. 10, p. 537.

[7] Pohl: *Archiv für exper. Physiologie und Pharmakologie,* 1893, Bd. 31, p. 298.

[8] Rajewsky: *Pflüger's Archiv,* 1875, Bd. 11, p. 122.

esters of the fatty acids (fusel oils), glycerin, and succinic acid are produced. Such fermentation may to a small extent take place in the intestine,[1] and likewise in the bladder (occurrence in diabetic urine). Pure alcohol is a colorless, almost odorless liquid, having a burning taste. It is a valuable solvent of resins, fats, volatile oils, bromine, iodine, and many medicaments.

Tinctures are alcoholic solutions of various drugs and salts.

Liqueurs are manufactured from alcohol properly diluted, and treated with sugar and characteristic ethereal oils and aromatics.

Distilled liquors are obtained by the distillation of the fermentative products of various substances, whiskey from corn and rye, rum from molasses, brandy from wine. The characterizing taste depends on the different ethereal and fusel oils.

Wines are produced from the natural fermentation of grape-juice. Sherry, madeira, and port are fortified by the further addition of alcohol and sugar.

Beer is made by converting the starch of barley into maltose and dextrin through diastase. To an aqueous solution of the above hops are added, and the whole is boiled. After the settling of precipitated proteid, etc., the clear supernatant fluid is drawn off and treated with yeast, with ultimate conversion into beer. The taste is furnished by the hops.

ALCOHOL IN THE BODY.—Alcohol in the stomach at first prevents the gelatinization necessary in proteid for peptic digestion, but this difficulty is of no great moment because the absorption of alcohol is rapid and complete. It makes the mucous membrane hyperæmic, promotes the absorption of accompanying substances (sugar, peptone, potassium iodide), and stimulates the flow of the gastric juice.[2] In this matter it acts as do other condiments (salt, pepper, mustard, peppermint),[3] but if there be too great an irritation on the mucous membrane there is less activity (dyspepsia). The rapid absorption gives to alcohol its quick recuperative effect after collapse, and its value in administering drugs, especially antidotes. Alcoholic beverages combining alcohol and flavor promote gastric digestion and absorption, but often stimulate the appetite in excess of normal requirement. Alcohol is burned in the body, but may also be found in the breath, perspiration, urine, and milk. Alcohol has no effect on proteid decomposition, but acts to spare fat from combustion.[4] The addition of 50 to 80 grams of alcohol to the food has no apparent effect on the nitrogenous equilibrium.[5] Alcohol in the body acts as a paralyzant on certain portions of the brain, destroying the more delicate degrees of attention, judgment, and reflective thought, diminishing the sense of weariness (use after great exertion—furnished to armies in the last hours of battle) and raising the self-esteem; it paralyzes the vaso-constrictor nerves, producing turgescence of the skin with accompanying feeling of warmth and thereby indirectly aiding the heart.[6] The higher alcohols, propyl, butyl, amyl (see p. 983) are more poisonous as the series ascends,[7] and are less vol-

[1] Macfadyen, Nencki, and Sieber: *Archiv für exper. Pathologie und Pharmakologie*, 1891, Bd. 28, p. 347.

[2] Brandl: *Zeitschrift für Biologie*, 1892, Bd. 29, p. 277.   [3] Brandl, *Op. cit.*, p. 292.

[4] See V. Noorden: *Pathologie des Stoffwechsels*, 1893, p. 227.

[5] Ström: Abstract in *Centralblatt für Physiologie*, 1894, Bd. 8, p. 582.

[6] Schmiedeberg: *Grundriss der Arzneimittellehre*, 2d ed., 1888.

[7] Gibbs and Reichert: *Archiv für Physiologie*, 1893, Suppl. Bd. p. 201.

atile, less easily burned, and therefore more tenaciously retained by the body, with more pernicious results.

Ethyl Ether, $C_2H_5.O.C_2H_5$.—This is formed by the action of sulphuric acid on alcohol, thus:

$$C_2H_5OH + H_2SO_4 = C_2H_5HSO_4 + H_2O.$$

$$C_2H_5HSO_4 + C_2H_5OH = (C_2H_5)_2O + H_2SO_4.$$
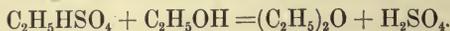
Ether is a solvent for fats, resins, and ethereal oils. Respired with air its action is like that of chloroform, producing temporary paralysis of the nerves and nervous centres. Since it boils at 35.5° its tension in the blood is always high, and it is probably not burned in the body to any great extent, but when present is eliminated through the breath.

Ethers in general are neutral and very stable bodies, and may be considered oxides of organic radicles. They may all be prepared by boiling the corresponding alcohol with sulphuric acid. *Mixed ethers*, in which the radicles are different, are prepared by boiling two different alcohols with sulphuric acid:
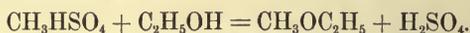
$$CH_3HSO_4 + C_2H_5OH = CH_3OC_2H_5 + H_2SO_4.$$
$$\text{Methyl-ethyl ether.}$$

Chloral Hydrate, $CCl_3CHO + H_2O$ or $CCl_3CH(OH)_2$.—This is the hydrated form of trichlor-ethyl aldehyde, CCl_3CHO, and is used as an anæsthetic. It is an interesting fact that when fed it partially reappears in the urine as *urochloralic acid*, which consists of trichlor-ethyl alcohol, CCl_3CH_2OH, combined with glycuronic acid (which see). This is a notable illustration of *reduction* in the body, the change from an aldehyde to an alcohol.

Acetic Acid, CH_3COOH.—Acetic acid, the second of the fatty-acid series, is found in the intestinal tract and in the feces, being a product of putrefaction (see p. 988). It is more easily burned than formic acid, and when absorbed is resolved into CO_2 and water. It is found in traces in the urine, the total amount of fatty acids normally present being 0.008 gram per day.[1] Like formic acid, and accompanied further by the higher acids of the series, it is present in the blood, sweat, and urine whenever there is an abnormal proteid decomposition (leucocythæmia, diabetes).

Acetic acid is the product of the oxidation of alcohol. This may be brought about through the presence of spongy platinum, or through the action of bacteria (*Mycoderma aceti*) on dilute alcohol (preparation of vinegar, souring of wine: for reaction see p. 976). Acetic acid, as well as other higher fatty acids, is one of the products derived from proteid through its putrefaction, its dry distillation, its fusion with potash, and its digestion with baryta water in sealed tubes. Formic, acetic, and propionic acids are products of dry distillation of sugar (formation of caramel). These facts are of importance in their relation to the question of the production of fat in the body. Acetic and the higher fatty acids are, further, products of the dry distillation of wood and of the fermentation of cellulose (see p. 976). Putrefaction of acetates may take place in the intestines, the reaction being as follows:

$$2CH_3COONa + 2H_2O = Na_2CO_3 + 2CH_4 + H_2O + CO_2.$$
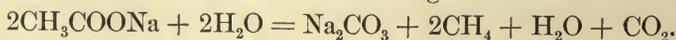
These products are similar to those in the marsh-gas fermentation of cellulose. *Vinegar*, whose acidity is due to acetic acid, is used as a condiment.

Acetyl-acetic Acid, or Aceto-acetic Acid, $CH_3.CO.CH_2.COOH$.—This

[1] V. Jaksch : *Zeitschrift für physiologische Chemie*, 1886, Bd. 10, p. 536.

may be considered as acetic acid in which one H atom is replaced by acetyl, $CH_3CO—$; or as β-keto-butyric acid. Treated with hydrogen it is reduced to β-oxybutyric acid ($CH_3.CHOH.CH_2.COOH$), which in turn may be oxidized to the original substance. Aceto-acetic acid readily breaks up into acetone and carbonic acid:

$$CH_3COCH_2COOH = CH_3COCH_3 + CO_2.$$

Aceto-acetic acid, acetone, and β-oxybutyric acid are found in the urine sometimes singly, sometimes together, but only as the result of a metabolism of the body's organized proteid (leucocythæmia, diabetes, fever, inanition), not of that of the proteid ingested. Indeed, these substances under the above circumstances seem to appear in the urine in direct proportion to the nitrogen present—in other words, to the proteid decomposition.[1] From their chemical relations already mentioned they may be regarded as of common origin, coming from the proteid molecule under peculiar conditions of metabolism, and in confirmation of this, Araki[2] has shown that on feeding β-oxybutyric acid it is oxidized and aceto-acetic acid and acetone may be detected in the urine. The production of the two acids seems to further a gradual neutralization of the blood, ultimately causing coma.[3] In the presence of these substances ammonia runs high in the urine, and in amounts proportional to their excretion[4] (compare p. 993).

Aceto-acetic acid gives to urine in the absence of phosphates a red coloration with ferric chloride (principle of the reaction of Gerhardt).

Amido-acetic Acid, or Glycocoll, $CH_2.NH_2.COOH$.—This is a substance obtained by boiling gelatin with acids or alkalies. It is found in human bile and in that of other animals combined with cholic acid and called glycocholic acid. Chittenden[5] has found glycocoll in the muscles of *Pecten irradians*. It is found in the urine combined with benzoic acid as hippuric acid after feeding benzoic acid or compounds which the body converts into benzoic acid. In a similar manner phenaceturic acid is found in the urine from the grouping together of glycocoll and phenyl acetic acid. Glycocoll and urea are to be obtained by the decomposition of uric acid through hydriodic acid. Glycocoll forms colorless crystals, soluble in water and having a sweet taste.

Glycocoll in the Body.—If glycocoll be fed it is absorbed and appears as urea in the urine. The fact that dogs, whose bile never contains glycocholic acid, nevertheless excrete hippuric acid after being fed with benzoic acid, indicates that glycocoll may be considered a normal nitrogenous decomposition product of proteid. Its easy cleavage from gelatin, a product manufactured from proteid in the body, confirms this.

Amido- Acids in General.—These acids, such as glycocoll, aspartic acid, glutamic acid, leucin, and tyrosin are found as putrefactive products of albumin and gelatin. In these acids the amido- group is very stable, and cannot be removed by boiling with KOH. They are all converted in the body into the amide of carbonic acid (urea). Amido- acids may in general be synthetically formed by heating mono-halogen compounds of the fatty acids with ammonia:

$$CH_2ClCOOH + NH_3 = CH_2NH_2COOH + HCl.$$

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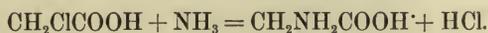
[1] Wright: *Grocers' Research Scholarship Lecture*, London, 1891; V. Noorden: *Pathologie des Stoffwechsels*, 1893, p. 178.

[2] *Zeitschrift für physiologische Chemie*, 1893, Bd. 18, p. 6.

[3] Münzer and Strasser: *Archiv für exper. Pathologie und Pharmakologie*, 1893, Bd. 32, p. 372.

[4] *Loc. cit.*   [5] *Annalen der Chemie und Pharmakologie*, 1875, Bd. 178, p. 266.

Methyl Amido-acetic Acid, or Sarcosin, $CH_5.NH.CH_2.COOH$.—This is not found in the body, but is derived from creatin, theobromin, and caffein by heating with barium hydroxide.

PROPYL COMPOUNDS.

Normal or Primary Propyl Alcohol, $CH_3CH_2CH_2OH$.—This is one of the higher alcohols formed in the fermentation of sugar, and on oxidation yields propyl aldehyde and propionic acid.

Propionic Acid, CH_3CH_2COOH.—Combined with glycerin this forms the simplest fat; salts of this acid feel fatty to the touch. Propionic acid is a product of the dry distillation of sugar, of the butyric-acid fermentation of milk-sugar, and of the putrefaction of proteid. It is said to be present in the sweat, in the bile, and sometimes in the contents of the stomach. Like others of the lower fatty acids, it may partially escape oxidation and appear in traces in the urine (see p. 980).

β-Acetyl Propionic Acid, or Levulic Acid, $CH_3COCH_2CH_2COOH$.—This is the next higher homologue to aceto-acetic acid. It has been obtained only by boiling sugars, especially levulose, with acid and alkalies, and since Kossel and Neumann[1] found that it is yielded by some nucleins they conclude that this indicates the presence of the carbohydrate radical in these nucleins.

Dimethyl Ketone, or Acetone, CH_3COCH_3.—This is found normally in the blood and urine, and in especially large quantities in patients suffering from an abnormal decomposition of organized proteid (see p. 981). During the first day of starvation by Cetti, the starvation artist, the amount of acetone in the urine rose to forty-eight times that of the day previous.[2] It may likewise appear in the breath, giving a characteristic odor. Acetone is a product of the dry distillation of tartaric and citric acids, of wood, and of sugar. Its occurrence in the urine, in diabetes, however, is not proportional in any way to sugar-metabolism or non-metabolism (see p. 981). Oxidized, acetone yields acetic and formic acids, whereas, treated with hydrogen, it is resolved into secondary propyl alcohol. When acetone is in the urine it is also found in the intestinal canal and in the feces, probably by passage through the intestinal wall.

BUTYL COMPOUNDS.

Normal Butyric Acid, $CH_3CH_2CH_2COOH$.—Butyric acid was first found in butter, combined with glycerin. When free it gives the rancid odor to butter, and likewise contributes to the odor of sweat. It has been detected in the spleen, in the blood, and in the urine, but usually only in traces. As a product of putrefaction of proteid, and especially of carbohydrates, it is found in the intestines and in the stomach when the acidity is insufficient to be bactericidal. It contributes to the unpleasant taste after indigestion, through the return of a small portion of the chyme to the mouth. In cheese it is a product of the putrefaction of casein.

If starch, sugar, or dextrin be treated with water, calcium carbonate, and

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[1] Verhandlung der Berliner physiologischen Gesellschaft, *Archiv für Physiologie,* 1894, p. 536.
[2] Fr. Müller: *Berliner klinische Wochenschrift,* 1887, p. 428.

foul cheese, the carbohydrates are slowly converted into a mass of calcium lactate. On further standing the lactic acid is resolved into butyric acid:

$$2CH_3CHOHCOOH = C_3H_7COOH + 4H + CO_2.$$
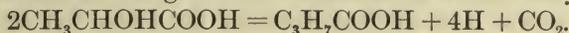
Lactic acid.

Calcium salts are found to putrefy more readily than others, and the carbonate is added above to neutralize any acids formed in the putrefactive process which might inhibit the action of the spores. This same fermentation takes place in the intestinal tract.

Iso-butyl Alcohol, $(CH_3)_2: CH.CH_2OH$.—This is found in fusel oil.

Iso-butyric Acid, $(CH_3)_2: CH.COOH$.—This is a product of proteid putrefaction and is found in the feces.

Pentyl Compounds.

Iso-pentyl Alcohol, or Amyl Alcohol, $(CH_3)_2CHCH_2CH_2OH$.—This is the principal constituent of fusel oil, producing the after-effects of distilled-liquor intoxication. The poisonous dose in the dog per kilogram for the different alcohols has been found to be—for ethyl alcohol 5–6 grams, for propyl alcohol 3 grams, for butyl alcohol 1.7 grams, for amyl alcohol 1.5 grams [1] (see p. 979).

Iso-pentoic or Iso-valerianic Acid, $(CH_3)_2CHCH_2COOH$.—This is found in cheese, in the sweat of the foot, likewise in the urine in small-pox, in typhus, and in acute atrophy of the liver. It is a product of proteid putrefaction, and has a most unpleasant odor.

Alcohols containing More than Five Carbon Atoms.

Of these, *cetyl alcohol*, $C_{16}H_{35}OH$, is found combined with palmitic acid in spermaceti; *cerotyl alcohol*, $C_{27}H_{55}(OH)$, is found as an ester in Chinese wax; and *melicyl alcohol*, $C_{30}H_{61}OH$, is combined with palmitic acid in beeswax.

Acids containing More than Five Carbon Atoms.

Caproic Acid, $C_5H_{11}COOH$.—This is formed from the putrefaction of proteid, being found in cheese and in feces; it may likewise be detected in the sweat. United with glycerin it occurs in butter-fat.

Iso-butyl Amido-acetic Acid, or Leucin, $(CH_3)_2: CH.CH_2.CHNH_2.COOH$.—This substance is a constant product of proteid putrefaction, is therefore found in cheese, and may likewise be obtained by boiling proteid or gelatin with sulphuric acid or with alkali. When fed it is converted into urea. When fed to birds the tissues decompose it with elimination of ammonia, which latter may be converted into uric acid by the liver.[2] It is said to occur in pancreatic juice. According to Kühne it is produced in trypsin proteolysis to the extent of 9.1 per cent. of the proteid used. Since this weakly alkaline medium in pancreatic digestion is especially favorable to bacterial activity, Kühne added antiseptic salicylate of sodium and still found leucin (and tyrosin). The same results are obtained with thymol. It is generally accepted that leucin (and tyrosin) are normal products of tryptic digestion. In certain diseases of the liver

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[1] Dujardin-Beaumetz et Audigé: *Comptes rendus*, vol 81, p. 19.

[2] Minkowski: *Archiv für exper. Pathologie und Pharmakologie*, 1886, Bd. 21, p. 85.

leucin (and tyrosin) appear in the urine, which may be interpreted to mean that these substances, normally produced from proteid metabolism in the tissues, are not normally burned but accumulate within the body, and are excreted (see below).

Another view, advanced by Von Noorden[1] and based on the unconfirmed experiments of Harris and Tooth,[2] claims that leucin and tyrosin are not found in tryptic digestion if bacteria be excluded. Leucin and tyrosin are found in yellow atrophy of the liver both in the urine and in the liver itself, under conditions indicating their production by bacteria and their non-combustion after production. In phosphorus-poisoning and acute anæmia leucin and tyrosin occur in the urine, but apparently without good ground for considering them of bacterial origin. Von Noorden argues that, as in yellow atrophy of the liver, the tissue-cells have become incapable of decomposing leucin and tyrosin, and these substances absorbed as products of intestinal putrefaction cannot be burned but are eliminated by the urine. That leucin is a product of proteid metabolism in the tissues has never been shown.

Leucin crystallizes in characteristic ball-shaped crystals. It was formerly supposed to be amido-caproic acid, but Schulze[3] has shown its true composition. Inactive leucin consists of a mixture of *d*- and *l*-leucin, and may be obtained by treating conglutin with $Ba(OH)_2$. The two leucins may be separated by fermentation of *d*-leucin with *Penicillium glaucum*. Cleavage of proteid by acids and by putrefaction seems to yield *d*-leucin.[4]

Caprylic, $C_8H_{16}O_2$, and Capric, $C_{10}H_{20}O_2$, Acids.—These are found as glycerin esters in milk-fat. They are likewise present in sweat and in cheese.

Palmitic, $C_{16}H_{32}O_2$, and Stearic, $C_{18}H_{36}O_2$, Acids.—As glycerin esters these two acids are found in the ordinary fat of adipose tissue, and in the fat of milk. The acids may occur in the feces, and are found combined with calcium in adipocere (p. 1002). Wool-fat consists in the cholesterin esters of these acids.

The bile contains palmitic, stearic, and oleic acids,[5] and to these have been attributed its very slight acid reaction.[6]

Compounds of the Alcohol Radicals with Nitrogen.

Amines.—These are bodies in which either one, two, or three of the hydrogen atoms in ammonia are replaced by an alcohol radical, and are termed respectively primary, secondary, and tertiary amines. Methyl, ethyl, and propyl amine bases are the products of proteid putrefaction. They resemble ammonia in their basic properties.

Methylamine, $NH_2(CH_3)$.—This is found in herring-brine. It has the fishy smell noted in decaying fish. It is a product of the distillation of wood and of animal matter. Feeding methylamine hydrochloride is said to cause the appearance of methylated urea in a rabbit's urine[7] (analogous to the formation of urea from ammonia salts):

$$2HCl.NH_2(CH_3) + CO_2 = OC(NHCH_3)_2 + 2HCl + H_2O.$$

According to Schiffer,[8] the body, probably through intestinal putrefaction, has the power of partially converting creatin into oxalic acid, ammonia, carbonic acid, and methylamine, which last is finally excreted as methylated urea in the urine.

[1] *Pathologie des Stoffwechsels*, 1893, p. 296.   [2] *Journal of Physiology*, 1888, vol. 9, p. 220.

[3] *Berichte der deutschen chemischen Gesellschaft*, 1891, Bd. 24, p. 669; also, Gmelin: *Zeitschrift für physiologische Chemie*, 1893, Bd. 18, p. 38.

[4] Gmelin: *Zeitschrift für physiologische Chemie*, 1893, Bd. 18, p. 28.

[5] Lassar-Cohn: *Ibid.*, 1894, Bd. 19, p. 571.

[6] Jolles: *Pflüger's Archiv*, 1894, Bd. 57, p. 13.

[7] Schiffer: *Zeitschrift für physiologische Chemie*, 1880, Bd. 4, p. 245.   [8] *Loc. cit.*

Ethylamine, $C_2H_5NH_2$, when fed as carbonate appears in part as ethylated urea in the urine.[1]

Trimethylamine, $N(CH_3)_3$.—Like ethylamine, this is found in herring-brine and among the products of proteid putrefaction and distillation. In the putrefaction of meat the first ptomaine appearing is cholin, which certainly is derived from lecithin; the cholin (see p. 986) gradually disappears, and in its place trimethylamine may be detected.[2]

COMPOUNDS WITH CYANOGEN.

The radicle NC— forms a series of bodies not unlike the halogen compounds. Owing to the mobility of the cyanogen group, Pflüger[3] has sought to attribute the properties of living proteid to its presence in the molecule, whereas in the dead proteid of the blood-plasma, for example, he imagines that the nitrogen is contained in an amido- group. When the cyanogen radical occurs in a compound in the form of $N{\equiv}C$— the body is called a nitril, when in the form of $C{\equiv}N$— an iso-nitril.

Cyanogen Gas, $NC-CN$.—A very poisonous gas.

Hydrocyanic Acid, HCN.—This is likewise a strong poison. Amygdalin is a glucoside occurring in cherry-pits, in bitter almonds, etc., together with a ferment called emulsin, which latter has the power of transforming amygdalin into dextrose, benzaldehyde, and hydrocyanic acid. Hydrocyanic acid, therefore, gives its taste to oil of bitter almonds, and it may likewise be detected in cherry brandy.

Potassium Cyanide, KCN.—This and all other soluble cyanides are fatal poisons.

Acetonitril, or Methyl Cyanide, CH_3CN.—This and its higher homologous nitrils are violent poisons. After feeding acetonitril in small doses, formic acid (see p. 978) and thiocyanic acid (see below) appear in the urine, the thiocyanic acid being a synthetic product of the ingested cyanogen radical, and the HS— group of decomposing proteid.[4] After feeding higher homologues of acetonitril or hydrocyanic acid, thiocyanide likewise appears in the urine. Since the amount of thiocyanide in the urine is normally very small, there is no reason for believing that cyanogen radicals similar to those described above are ever, to any great extent, cleavage-products of proteid.[5] Through intravenous injections of sodium sulphide, and especially of sodium thiosulphate, poisonous cyanogen compounds may be administered much beyond the dose ordinarily fatal:[6]

$$NaCN + SO_2 < {SNa \atop ONa} + O = NCSNa + Na_2SO_4.$$
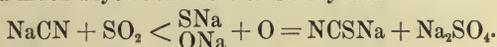
Cyanamide, $NC.NH_2$.—This is a laboratory decomposition-product of creatin, but does not occur in the body. It is poisonous when administered. When boiled with dilute sulphuric or nitric acids it is converted into urea:

$$NCNH_2 + H_2O = H_2NCONH_2.$$
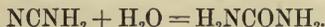
It is to be remembered that creatin in the body is not converted into urea.

Ammonium Cyanate, $OCN(NH_4)$.—Boiling ammonium cyanate converts it into urea. This was shown by Wöhler in 1828, and was the first authoritative laboratory production of a body characteristic of living organisms:

$$OCN(NH_4) = OC(NH_2)_2.$$
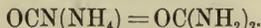
This reaction illustrates Pflüger's idea of the transformation of the cyanogen radical in living proteid into the amido- compound in the dead substance. According to Hoppe-

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[1] Schmiedeberg: *Archiv für exper. Pathologie und Pharmakologie*, 1877, Bd. 8, p. 5.

[2] Brieger : Abstract in *Jahresbericht über Thierchemie*, 1885, p. 101.

[3] *Pflüger's Archiv*, 1875, Bd. 10, p. 251.

[4] Lang: *Archiv für exper. Pathologie und Pharmakologie*, 1894, Bd. 34, p. 247.

[5] *Op. cit.,* p. 256.

[6] Lang : *Archiv für exper. Pathologie und Pharmakologie*, 1895, Bd. 36, p. 75.

Seyler the urea-formation in the body is as indicated in the above reaction, but that no cyanic acid or ammonium cyanate is to be detected on account of their extreme instability.

Potassium Thiocyanide, NCSK.—This substance is usually found in human saliva and in the urine. Since it contains nitrogen and sulphur its original source must be from proteid. The amount in the urine is probably wholly and quantitatively derived from that in the saliva.[1] If thiocyanides be fed, they appear quickly in the urine without change. Thiocyanides are less poisonous than the simple cyanides (see discussion under Acetonitril above). Thiocyanides give a red color with ferric chloride in acid solution.

DIATOMIC ALCOHOL RADICALS.

Thus far only derivatives of monatomic radicals have been discussed; next in order follow diatomic alcohol radicals, represented by the formula C_nH_{2n}, and including the bodies *ethylene*, $H_2C = CH_2$, *propylene*, $CH_3 — HC = CH_2$, etc. This set of hydrocarbons is called the olefines. The first series of compounds which are of physiological interest are the amines of the olefines.

AMINES OF THE OLEFINES.

These include the group of *ptomaïnes*—basic substances which are formed from proteid through bacterial putrefaction. Those which are poisonous are called *toxines*. These bodies are diamines of the olefines, and have been investigated especially by Brieger.[2]

Tetramethylene-diamin, or Putrescin, $H_2N.CH_2.CH_2.CH_2.CH_2.NH_2$.—This compound is found in putrefying proteid, and has been detected in the urine and feces in cystitis.

Pentamethylene-diamin, or Cadaverin, $H_2N.C_5H_{10}.NH_2$.—This is found with putrescine wherever produced. They are both found in cultivations of Koch's cholera bacillus and in cholera feces. In cystitis they are a result of special infection of the intestinal tract, are principally excreted in the feces, but are partially absorbed, and prevent, perhaps through chemical union, the burning of cysteïn normally produced.[3] Diamines are not normally present in the urine.

Neuridin and Saprin.—These are isomers of cadaverin and are produced by the same putrefactive processes.

Cholin.—This is trimethyl oxyethyl ammonium hydroxide,

$$(CH_3)_3 \equiv N < {OH \atop CH_2CH_2OH}$$
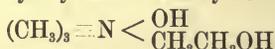
and has its source in lecithin decomposition, and putrefaction (see p. 1001).

Muscarin, or Oxycholin.—This is a violent heart-poison, and may be obtained by treating cholin with nitric acid.

Neurin.—This is trimethyl-vinyl ammonium hydroxide, $(CH_3)_3 \equiv N < {OH \atop CH = CH_2}$, and is derived from lecithin. Theoretically it may be considered as derived from cholin, with the elimination of a molecule of water, but it has never been shown that bacteria make this conversion. It is a powerful poison.

DERIVATIVES OF DIATOMIC ALCOHOLS.

Taurin, or Amido-ethyl Sulphonic Acid, $H_2N.CH_2.CH_2.SO_3H$.—This has been detected in muscle,[4] in the spleen, and in the suprarenal capsules.

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[1] Gscheidjen: *Pflüger's Archiv,* 1877, Bd. 14, p. 411.

[2] Abstract, *Jahresbericht über Thierchemie,* 1885, p. 101.

[3] Baumann und Udranszky: *Zeitschrift für physiologische Chemie,* 1889, Bd. 13, p. 562, and 1891, Bd. 15, p. 77.

[4] Reed, Kunkenberg, and Wagner: *Zeitschrift für Biologie,* 1885, Bd. 21, p. 30.

It is likewise a usual constituent of the human bile in combination with cholic acid, the salt present being known as sodium taurocholate. Taurin is of proteid origin as is shown by its nitrogen and sulphur content. Little is known regarding its fate in the body, except as it indicated through the behavior of its sulphur atom (see p. 951).

The Biliary Salts.—Taurin and glycocoll are found in the bile of cattle in combination with *cholic acid* ($C_{24}H_{40}O_5$). In human bile, according to Lassar-Cohn,[1] there is more *fellic acid* ($C_{23}H_{38}O_4$) present than cholic, and there is likewise present some *choleic acid*, ($C_{24}H_{40}O_2$). These acids are of similar chemical structure, though what the structure is, is unknown. Still other acids occur in the bile of pigs, geese, etc. Taurin and glycocoll form compounds with these acids, the sodium salts of which usually make up the major part of the solids of the bile. It has been shown that glycocoll and taurin are found in various parts of the body. Cholic, fellic, etc. acids are only found as products of hepatic activity. In a dog with a biliary fistula the solids of the bile increase on feeding much meat, but the hourly record of the solids compared with the nitrogen in the urine shows that the great production of biliary salts continues after the nitrogen in the urine has begun to decrease.[2] The experiments of Feder[3] have shown that the greater part of the *nitrogen* in proteid eaten by a dog leaves the body within the first fourteen hours, whereas the excretion of the *non-nitrogenous* moiety is more evenly distributed over twenty-four hours. It may be fairly concluded that cholic and fellic acids are produced from the non-nitrogenous portion, or from sugar or fat.[4] Furthermore Tappeiner[5] has shown that cholic acid on oxidation yields fatty acids. A synthesis may therefore be effected in the liver between the non-nitrogenous cholic acid formed in the liver from fat or materials convertible into fat, and glycocoll and taurin formed from proteids, whether the latter be produced in the liver or brought to it from the tissues by the blood. That the liver is the place for the synthesis is shown by the fact that the biliary salts do not collect in the body after extirpation of the liver.

In the intestine either the acid of the gastric juice or bacteria may split up the biliary salt through hydrolysis:

$$C_{26}H_{43}NO_6 + H_2O = C_2H_5NO_2 + C_{24}H_{40}O_5.$$
Glycocholic acid.   Glycocoll.   Cholic acid.
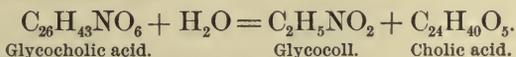
Taurin and glycocoll may be absorbed, while cholic acid is precipitated if in an acid medium, but may be dissolved and absorbed in an alkaline intestine. Hence cholic acid, fellic acid, etc., may often be found in the feces. Meconium, that is, the fecal matter of the fetus, contains quantities of the biliary salts, but unaltered, since putrefaction is absent in the fetus. Kühne has described *dyslysin* as a putrefactive product of cholic acid, but its existence is denied by Hoppe-Seyler and Voit. In *icterus* (jaundice), a condition in

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[1] *Zeitschrift für physiologische Chemie*, 1894, Bd. 19, p. 570.
[2] Voit : *Zeitschrift für Biologie*, 1894, Bd. 30, p. 545.   [3] *Ibid.*, 1881, Bd. 17, p. 531.
[4] Voit, *Op. cit.*, p. 556.   [5] *Zeitschrift für Biologie*, 1876, Bd. 12, p. 60.

which the biliary salts return to the blood from the liver, they are burned in the body, sometimes so completely that none appear in the urine. They have the power of dissolving hæmoglobin from the blood-corpuscles, and in consequence the urine may be highly colored, perhaps from bilirubin.[1]

Pettenkofer, experimenting once on the conversion of sugar into fat, warmed together cane-sugar, bile, and concentrated sulphuric acid. He obtained no fat, but a strong violet coloration. This is "Pettenkofer's test" for biliary acids (cholic acid, fellic acid, etc.). This coloration is likewise given by proteid, oleic acid, and other bodies. The test of Neukomm, however, is said to be absolutely characteristic. Here a drop of a substance containing biliary acids is placed on a small white porcelain cover, with a drop of dilute cane-sugar solution, and one of dilute sulphuric acid; the mixture is then very carefully evaporated over a flame and leaves a brilliant violet stain.

Oxy- Fatty Acids, Lactic-acid Group.

These are diatomic monobasic acids of the glycols. A glycol is a diatomic alcohol. The oxy- fatty acids have the general formula $C_nH_{2n}O_3$, and include:

Carbonic acid, CH_2O_3. Oxy-butyric acid, $C_4H_8O_3$.
Glycollic acid, $C_2H_4O_3$. Oxy-valerianic acid, $C_5H_{10}O_3$.
Lactic acid, $C_3H_6O_3$. etc.

Carbonic Acid, or Oxy-formic Acid, $HO.CO.OH$.—This is, in reality, a dibasic acid on account of the symmetric structure of the two —OH radicals. It has already been considered (see p. 1003).

Lactic Acids, or Oxy-propionic Acids.—Of these there are two isomeres, which vary in the position of their —OH group, the α- and β- lactic acids. Physiology is concerned only with the first.

α-Lactic Acid, or Ethidene Lactic Acid, $CH_3.CHOH.COOH$.—This is called *fermentation lactic acid*, being a product of the fermentation of carbohydrates (see p. 982):

$$C_6H_{12}O_6 = 2C_3H_6O_3.$$
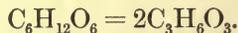
On lactic fermentation of milk-sugar depends the souring of milk. This fermentation does not take place in the presence of sufficiently acid gastric juice, but it is very active in the more nearly neutral (or alkaline) intestine. After a meal which includes carbohydrates the intestinal contents may remain quite distinctly acid down to the ileo-cæcal valve, due to acetic and lactic acid production, to such an extent even that proteid putrefaction is inhibited, as indicated by the total absence of leucin and tyrosin.[2] It has been noticed that the fecal excrements after a carbohydrate diet react acid, after proteid diet alkaline. The acid reaction is due chiefly if not wholly to acetic acid, since lactic acid, being the stronger acid, is first neutralized by the intestinal alkali. Lactic acid, when absorbed, is completely burned in the body. Lactic-acid fermentation between the teeth dissolves the enamel, and gives bacteria access to the interior. The fermentation lactic acid is inactive to polarized light, and, since

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[1] Hoppe-Seyler: *Physiologische Chemie*, 1877, p. 476.
[2] Macfadyen, Nencki, und Sieber: *Archiv für exper. Pathologie und Pharmakologie*, 1891, Bd. 28, p. 347.

it has in its formula an asymmetric carbon atom,[1] it is necessary to assume that it consists of an equal mixture of right and left ethidene lactic acid. On standing with *Penicillium glaucum* the left lactic acid is destroyed more freely than is the right, and the solution rotates polarized light to the right.[2]

The right ethidene lactic acid, called also sarco- or para-lactic acid, is that which is found in muscle, blood, in various blood-glands, in the pericardial fluid, and in the aqueous humor. Likewise it is found in the urine after strenuous physical effort, after CO-poisoning, in yellow atrophy of the liver, in phosphorus-poisoning, in trichinosis, and in birds (geese and ducks) after the liver has been extirpated. It is sometimes present in diabetic urine. Para-lactic acid is a normal constituent of the blood and increases in amount after work or tetanus. It accumulates in the dying muscle (*rigor mortis*), causing the formation of KH_2PO_4, which gives the acid reaction and causes coagulation.[3] Some believe that free lactic acid itself is present and aids in the coagulation. Regarding its origin it has been shown that it increases in amount in the dying muscle without simultaneous decrease in the amount of glycogen.[4] On extirpation of the liver in geese,[5] ammonia and lactic acid replace the customary uric acid in the excreta, and previous ingestion of carbohydrates or of urea will not increase the amount of lactic acid. The lactic acid excreted is proportional in amount to the proteid destroyed and to the ammonia present. It may fairly be concluded that it owes its origin to proteid.

Hoppe-Seyler [6] says that lactic acid appears in the urine only when there is insufficient oxidation in the body, and attributes its derivation to the decomposition of glycogen. In CO-poisoning Araki [7] finds as much as 2 per cent. of lactic acid (reckoned as zinc lactate) in a rabbit's urine. Minkowski,[8] on the other hand, denies the insufficient-oxidation theory, and maintains that the destruction of lactic acid depends on a specific property of the

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[1] An asymmetric carbon atom is one in which the four atoms, or groups of atoms, united to

it are all different. In lactic acid we find the following grouping, $H-\underset{\underset{COOH.}{|}}{\overset{\overset{CH_3}{|}}{C}}-OH$. The central

carbon represents the asymmetric atom. Such an arrangement is always optically active. One is able to conceive the arrangement of the atoms in space, according to the above grouping, or

as follows: $HO-\underset{\underset{COOH}{|}}{\overset{\overset{CH_3}{|}}{C}}-H$. This latter represents a different configuration. The two arrange-

ments are optically antagonistic. A mixture of the two is optically inactive. The reader is referred to a text-book on general chemistry for the suggestive illustrations of the tetrahedral space pictures.

[2] *Berichte der deutschen chemischen Gesellschaft*, Bd. 16, p. 2720.

[3] Astaschewski: *Zeitschrift für physiologische Chemie*, 1880, Bd. 4, p. 403; Irisawa, *Ibid.*, 1893, Bd. 17, p. 351.

[4] Boehm: *Pflüger's Archiv*, 1880, Bd. 23, p. 44.

[5] Minkowski: *Archiv für exper. Pathologie und Pharmakologie*, 1886, Bd. 21, p. 41.

[6] *Festschrift zu R. Virchow's 70. Geburtstag.*

[7] *Zeitschrift für physiologische Chemie*, 1894, Bd. 19, p. 426.

[8] *Loc. cit.*, and *Archiv für exper. Pathologie und Pharmakologie*, 1893, Bd. 31, p. 214.

liver, the normal action being either destruction in the liver itself or in other organs through the medium of a substance (enzyme?) produced in the liver.

One may interpret Araki's experiment as showing that considerable quantities of lactic acid are constantly produced in metabolism, but are normally swept away and burned; the CO-poisoning would prevent the normal combustion. The accumulation in muscle after stoppage of blood-current (*rigor mortis*) would then be only a continuation of the normal process of decomposition.

Cystein, *a*-Amido-*a*-thiopropionic Acid.—This substance has the formula

$$CH_3-\underset{\underset{SH}{|}}{\overset{\overset{NH_2}{|}}{C}}-COOH.$$
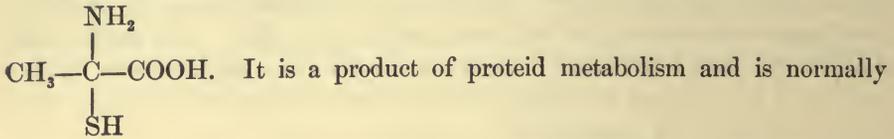
It is a product of proteid metabolism and is normally destroyed in the body. On the introduction of a halogen derivative of benzol into the body, compounds are formed with cystein, called *mercapturic acids,* which appear in the urine:

$$CH_3-\underset{\underset{SH}{|}}{\overset{\overset{NH_2}{|}}{C}}-COOH + C_6H_5Br + O = CH_3-\underset{\underset{SC_6H_4Br.}{|}}{\overset{\overset{NH_2}{|}}{C}}-COOH + H_2O.$$
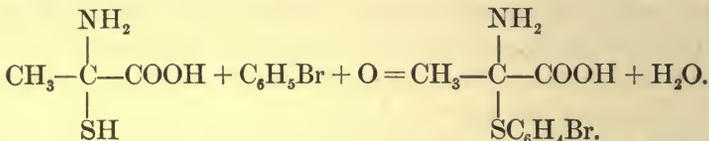
Bromophenyl-mercapturic acid.

This proves that cystein (like glycocoll, for example) is at least an intermediary and possibly a primary product of proteid metabolism (see p. 951). If cystein be fed, the greater part (two-thirds) of the sulphur appears in the urine as sulphuric acid, the rest as neutral sulphur. *Thiolactic acid* has been found [1] as a decomposition product of horn. Baumann [2] demonstrates the reduction of cystein to thiolactic acid, shows that the latter yields an odor of ethyl sulphide on evaporation, and asks if thiolactic acid be not the mother substance of Abel's compound (see p. 951):

$$CH_3-\underset{\underset{SH}{|}}{\overset{\overset{NH_2}{|}}{C}}-COOH + H_2 = CH_3CH(SH)COOH + NH_3.$$
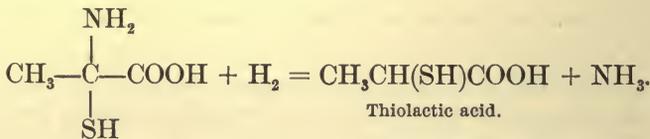
Thiolactic acid.

Cystein itself is never directly detected in the urine or in the body.

Cystin, Dithio-diamido-ethidene Lactic Acid.—Cystein is converted by atmospheric oxygen into cystin:

$$2CH_3-\underset{\underset{SH}{|}}{\overset{\overset{NH_2}{|}}{C}}-COOH + 2O = \underset{CH_3-CSNH_2-COOH}{\overset{CH_3-CSNH_2-COOH}{|}}$$
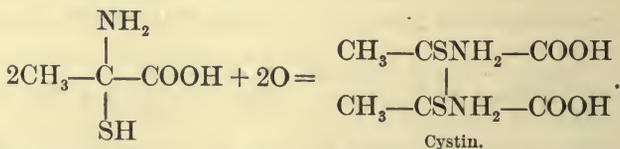
Cystin.

Cystin is very insoluble in water. In particular cases it appears in considerable

[1] Suter: *Zeitschrift für physiologische Chemie,* 1895, Bd. 20, p. 564.
[2] Baumann: *Ibid.,* 1895, Bd. 20, p. 583.

quantities as a urinary sediment, still more rarely as a stone in the bladder (see p. 986). It is lævo-rotatory.

It is reported [1] that bodies having the composition C—S—H (thio- acids, mercaptans) may form sulphuric acid, while most of those having the composition $\equiv$C—S—C$\equiv$ (ethyl sulphide) are not oxidized in the body.

β-Oxybutyric Acid, $CH_3CHOHCH_2COOH.$—A lævo-rotatory acid (see p. 981).

AMIDO- DERIVATIVES OF CARBONIC ACID.

$$OC{<}^{OH}_{OH}. \qquad OC{<}^{NH_2}_{OH}. \qquad OC{<}^{NH_2}_{NH_2}.$$

Carbonic acid.   Carbamic acid.   Carbamide.
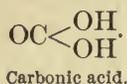
Carbamic Acid.—This is not known free, but its calcium salts have been found, especially in herbivorous urine, and its presence in the blood as ammonium carbamate is maintained.[2] The latter has been obtained by Drechsel [3] by oxidizing glycocoll and leucin in ammoniacal solution, and he has converted it into urea by electrolysis. From these facts he concludes that ammonium carbamate is the antecedent of urea.

Ammonium carbamate is formed by the direct union of ammonia with carbonic oxide in their nascent states, and is therefore found in commercial ammonium carbonate and as the product of the oxidation of the amido- compounds above mentioned :

$$2NH_3 + CO_2 = OC{<}^{NH_2}_{ONH_4}.$$
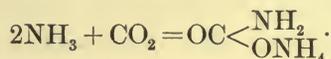
Water converts it into ammonium carbonate :

$$OC{<}^{NH_2}_{ONH_4} + H_2O = OC{<}^{ONH_4}_{ONH_4}.$$
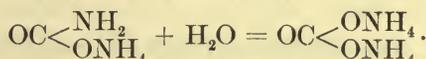
Carbamide, or Urea, $OC(NH_2)_2.$—This is the principal end-product of the nitrogenous portion of proteid in all mammals, being found in considerable concentration in the urine. It may be detected in the blood in traces, in lymph, and in the liver, but Liebig could find no trace of it in muscle. In uræmia it may collect in all tissues of the body, and may then be excreted in slight amount by the gastric and intestinal juices. It is given off in profuse sweating, though only in small proportion to that lost in the urine.

Preparation.—(1) Like other amides, by heating ammonium carbonate ; further, by the electrolysis of, or by heating, ammonium carbamate :

$$OC{<}^{ONH_4}_{ONH_4} = OC{<}^{NH_2}_{NH_2} + 2H_2O.$$

$$OC{<}^{NH_2}_{ONH_4} = OC{<}^{NH_2}_{NH_2} + \cdot H_2O.$$
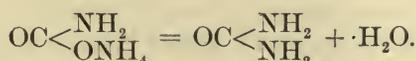
[1] W. J. Smith : *Pflüger's Archiv*, 1894, Bd. 55, p. 542, and 1894, Bd. 57, p. 418.

[2] Drechsel : *Ludwig's Arbeiten*, 1875, p. 172 ; Drechsel und Abel, *Archiv für Physiologie*, 1891, p. 242.

[3] *Loc cit.*

(2) Through the union of ammonia with carbonyl chloride:

$$OCCl_2 + 2NH_3 = OC(NH_2)_2 + 2HCl.$$
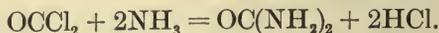
(3) By evaporating an aqueous solution of ammonium cyanate:

$$O:C:N.NH_4 = OC(NH_2)_2.$$
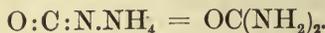
This was Wöhler's notable preparation in 1828 of an "organic" compound, a product of life, without the aid of a "vital force."

(4) As a decomposition product of guanin, xanthin, creatin, uric acid, etc.

(5) From proteid, through hydrolytic cleavage [1] (see p. 994). This origin has not as yet been confirmed.

Properties.—Urea is a weak base, of great stability when within the alkaline fluids and tissues of the body. It is soluble in water in all proportions, very soluble in hot, less so in cold alcohol, whence it crystallizes in needle-like forms. It melts at 132° and recrystallizes on cooling. Heated higher it is converted into biuret, a substance which gives a violet color with dilute cupric sulphate in a sodium-hydrate solution (called the biuret reaction):

$$2OC{<}_{NH_2}^{NH_2} = {OC{<}_{NH}^{NH_2} \atop OC{<}_{NH_2}} + NH_3.$$
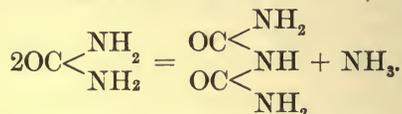
Heating urea with water over 100° in sealed tubes, boiling it with alkalies or acids, bacterial action (see p. 956), all convert it through hydrolysis into carbonic oxide and ammonia. Such decomposition may take place in the stomach in uræmia.[2] Nitrous oxide breaks up urea, thus:

$$OC(NH_2)_2 + 2HNO_2 = CO_2 + 3H_2O + 4N,$$
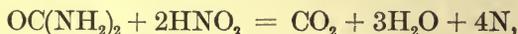
and hypobromite of soda acts in like manner in the presence of alkali:

$$OC(NH_2)_2 + 3NaBrO = CO_2 + 2H_2O + 2N + 3NaBr.$$

The alkali present absorbs the CO_2, and the volumes of N afford a measure for the amount of urea present (method of Hüfner, apparatus by Doremus).

Urea combines with nitric acid to form urea nitrate, $OC(NH_2)_2.HNO_3$, which is insoluble in nitric acid. Urea oxalate, which is formed in similar manner by the combination of urea with oxalic acid, is insoluble in water. Many combinations with metallic salts have been prepared, of which one with mercuric nitrate, of uncertain formula, is the basis of Liebig's method of titration for urea.

Urea in the Body.—This subject has been discussed under Nutrition. It can only be briefly considered here. When urea is fed it is rapidly excreted in the urine. The excreted nitrogen of proteid appears in mammalia in greater part as urea. Amido- products of proteid decomposition, glycocoll, leucin, aspartic acid, uric acid, when fed are converted by the body into urea. So likewise are ammonium carbonate, lactate, and tartrate. Ammonium chloride, on

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[1] Drechsel: *Archiv für Physiologie*, 1891, p. 261.
[2] Voit: *Zeitschrift für Biologie*, 1868, Bd. 4, p. 150.

account of the strong acid radical, passes through carnivora unchanged, but in herbivora, the blood of which is more strongly alkaline, a certain part of the ammonia is converted first into carbonate and then into urea. This conversion of ammonium carbonate into urea is of striking interest. Artificial irrigation of a liver with blood containing ammonium carbonate increases the urea in the blood, while similar treatment of muscle or kidney shows no such results.[1] In other experiments it has been shown that ammonium salts appear in the urine after feeding acids to carnivora, and that in disease in which acids are produced (lactic, aceto-acetic, oxybutyric acids) ammonia accompanying them is found in the urine, in all cases representing that ordinarily converted into urea. In disease of the liver (cirrhosis, phosphorus-poisoning) ammonia is found in the urine above the normal. Admitting the fact that ammonium carbonate (and carbamate likewise) may be converted into urea by the liver, there is no ground for believing that this is the normal process for the production of the whole amount of urea, nor is there at present any measure of the amount of ammonium-salts produced in the body. The liver may be very completely destroyed by disease, and large quantities of urea still be excreted.[2] In *geese* extirpation of the liver has no effect on the urea excreted, therefore in geese it is formed elsewhere.[3] For aught that is known, therefore, urea may be formed in other organs than the liver, and it is not at all improbable that it is formed in all organs where proteid decomposition is progressing. The greater part of urea from proteid is eliminated in the dog fourteen hours after his meal (see p. 987).

Guanidin, $HN:C<{NH_2 \atop NH_2}$. This is the imide of urea, and has been obtained by the oxidation of guanin. It unites with alcohol and acid radicals—forming, for example, methyl guanidin, $HNC<{NH_2 \atop NHCH_3}$, and guanidin acetic acid, $HN<{NH_2 \atop NHCH_2COOH}$.

Creatin, or Methyl Guanidin Acetic Acid, $HNC<{NH_2 \atop N(CH_3)CH_2COOH}$. Creatin is a product of proteid decomposition and found in muscle to the extent of 0.3 per cent., in traces in the blood, and in varying amounts in the urine. It is the principal constituent of meat-extracts (Liebig's). Creatin may be formed synthetically by the union of cyanamide with sarcosin, and it may be broken up into these constituents by boiling with barium hydrate, but the cyanamide is immediately converted into urea through the addition of water :

$$H_2N.CN + HN(CH_3)CH_2COOH = HN:C<{NH_2 \atop N(CH)_3CH_2COOH}.$$

Cyanamide.   Sarcosin.   Creatin.

Creatin, however, is not converted into urea in the body if fed, but is excreted in the urine as creatinin.[4] The amount of creatinin found in the urine

[1] Von Schroeder : *Archiv für exper. Pathologie und Pharmakologie,* 1882, Bd. 15, p. 364.

[2] Marfort : *Ibid.,* 1894, Bd. 33, p. 71.

[3] Minkowski : *Ibid.,* 1886, Bd. 21, p. 62.

[4] Voit : *Zeitschrift für Biologie,* 1868, Bd. 4, p. 114.

corresponds normally to the amount of creatin contained in the meat food ; in starvation urine it is proportional in amount to the proteid (muscle) destroyed, being present even on the thirtieth day (experiment on Succi[1]); and it is present only in traces, or not at all, in the urine of milk-fed children (creatin-free food). In convalescence creatin is said to be retained, possibly for the building of new muscle.[2] There is no reason for believing that much creatin is ever formed in the body.

Creatin gives its flavor to meat. If gently heated it gives the odor of roasting beef. Creatinin in the urine reduces alkaline solutions of copper salts (care must be taken, therefore, in making the sugar test after using meat extracts). The action of creatin is simply that of a pleasant-tasting, pleasant-smelling substance, which prepares the stomach for food but has no nourishing value *per se*. It is considered by some to be a nerve-stimulant.

Creatinin, or Glycolyl Methyl Guanidin.—Heating creatin with acids changes it into creatinin with loss of water, and having the formula

$$HN:C \begin{cases} NH-CO \\ \quad\quad | \\ N(CH_3)CH_2 \end{cases}.$$

Warming at 60° with phosphoric acid causes this conversion. In like manner when the kidney prepares an acid urine, creatin becomes creatinin : if the acid reaction be effaced through feeding alkaline salts the creatin is excreted unchanged.[3] Creatinin with chloride of zinc forms a characteristic very insoluble white powder of creatinin zinc chloride, $(C_4H_7N_3O)_2.ZnCl_2$.

Lysatin, $C_6H_{13}N_2O_2$, and Lysatinin, $C_6H_{11}N_3O_2$.—These substances are obtained, like lysin (see below), from the hydrolytic cleavage of proteid, as for example from casein or conglutin heated with hydrochloric acid and zinc chloride ; they are probably likewise produced in trypsin digestion.[4]

According to Drechsel[5] they are homologues of creatin and creatinin, and therefore should yield urea on heating with barium hydroxide. This is Drechsel's method of direct production of urea from proteid by hydrolytic cleavage.

Diamido- Fatty Acids.—Of these four have been described :

Diamido-acetic Acid, $CH(NH_2)_2COOH$.—This was found by Drechsel[6] among other compounds after heating casein in sealed tubes with concentrated hydrochloric acid at 140°. *Diamido-propionic acid* has not been found in the body.

Diamido-valeric Acid, or Ornithin, $C_4H_7(NH_2)_2COOH$.—This has been detected by Jaffe in the urine and excrements of fowls.

a-ε-**Diamido-caproic Acid, or Lysin,** $CH_2NH_2CH_2CH_2CH_2CHNH_2$-COOH.—This is a hydrolytic cleavage product of casein after boiling with hydrochloric acid, or baryta water,[7] and may be similarly obtained from gela-

[1] Luciani : *Das Hungern*, Leipzig, 1890, p. 144.

[2] Von Noorden : *Pathologie des Stoffwechsels*, 1893, p. 169.

[3] Voit : *Zeitschrift für Biologie*, 1868, Bd. 4, p. 150.

[4] See Drechsel, and his pupils Fisher, Siegfried, and Hedin : *Archiv für Physiologie*, 1891, p. 248 *et seq*.

[5] *Op. cit.*, p. 261.   [6] Abstract in Maly's *Jahresbericht über Thierchemie*, 1892, p. 9.

[7] Drechsel : *Archiv für Physiologie*, 1891, p. 248.

tin, from vegetable proteid (conglutin), and from the pancreatic digestion of fibrin.[1]

ALLOXURIC BODIES AND BASES.

The alloxuric bodies comprise those containing in combination two radicals, one of *alloxan*, $OC < \begin{matrix} NH - CO \\ NH - CO \end{matrix} > CO$, the other of urea. The skeletal structure of all alloxuric bodies may be written thus:

$$
\begin{matrix}
N-C & | \\
C \quad\quad C & |-N \\
N-C & |-N
\end{matrix} > C
$$

Alloxan. Urea.
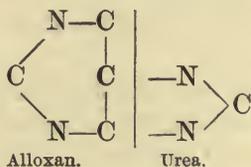
These bodies fall into three groups, that of hypoxanthin, of xanthin, and of uric acid. Bodies belonging to the first two groups are called *alloxuric bases*, or more commonly *xanthin bases*, or *nuclein bases*, because they are derived from nuclein. The strong family analogy of the three groups is shown by the following reactions—results of heating with hydrochloric acid in sealed tubes at 180° to 200°:[2]

$$C_5H_4N_4O + 7H_2O = 3NH_3 + C_2H_5NO_2 + CO_2 + 2CH_2O_2.$$

Hypoxanthin. Glycocoll. Formic acid.

$$C_5H_4N_4O_2 + 6H_2O = 3NH_3 + C_2H_5NO_2 + 2CO_2 + CH_2O_2.$$

Xanthin.

$$C_5H_4N_4O_3 + 5H_2O = 3NH_3 + C_2H_5NO_2 + 3CO_2.$$
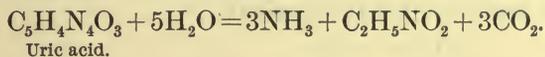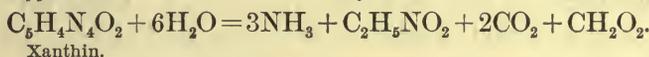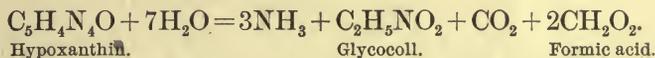
Uric acid.

Reference to the formulæ below will show that the molecules of CO_2 given off correspond to the number of CO radicals in the alloxuric body, while the molecules of formic acid correspond to the number of CH groups.

(a) HYPOXANTHIN BASES.

Hypoxanthin, or Sarcin,

$$HC \begin{matrix} NH - C - H \\ \quad\quad\quad C - NH \\ N - C = N \end{matrix} > CO.$$

—This is found in
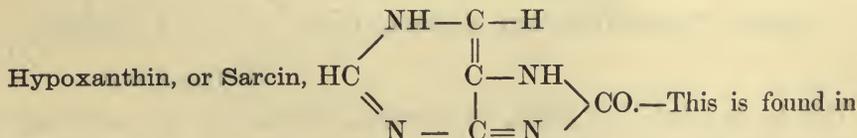
small amounts in the tissues and fluids of the body and in the urine. The action of water or dilute acids on nuclein yields hypoxanthin.[3]

Adenin, or Imidosarcin,

$$HC \begin{matrix} NH - C - H \\ \quad\quad\quad C - NH \\ N - C = N \end{matrix} > CNH.$$

—This is found

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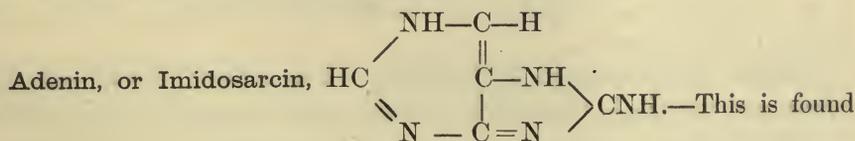
[1] For literature on these diamido- fatty acids see Klebs : *Zeitschrift für physiologische Chemie,* 1895, Bd. 19, p. 301.

[2] Krüger: *Ibid.,* 1894, Bd. 18, p. 463.   [3] Kossel : *Ibid.,* 1881, Bd. 5, p. 268.

in the tissues and fluids of the body and in the urine. It is, like hypoxanthin, a decomposition product of nuclei.[1] It is converted into hypoxanthin through the action of nitrous acid.

(b) Xanthin Bases.

Xanthin,
$$OC \overset{NH-C-H}{\underset{NH-C=N}{\diagup \overset{\parallel}{C-NH}\diagdown}}CO.$$
—This substance, like the two last
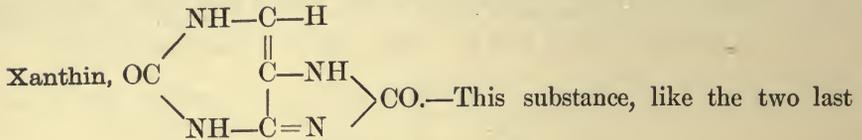
named, is found in the tissues and the fluids of the body, and is a decomposition product of nuclein. Occasionally it occurs in the form of a urinary calculus, as a stone of exceptional hardness.

Monomethyl Xanthin, or Heteroxanthin, $C_6H_6N_4O_2$.—This has likewise been detected in the urine (see Caffeïn).

Theobromin, Dimethyl Xanthin, or Paraxanthin.—

$$O=C \overset{NCH_3-C-H}{\underset{NH-C=N}{\diagup \overset{\parallel}{C-NCH_3}\diagdown}}CO.$$
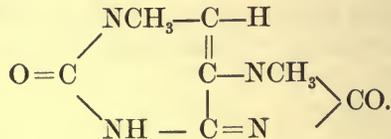
This is the principal alkaloid in cacao (chocolate). When fed it is in part excreted as monomethyl xanthin in the urine (see Caffeïn). Its silver compound treated with methyl-iodide yields caffeïn.

Theophyllin, $O=C \overset{NCH_3-C-H}{\underset{NCH_3-C=N}{\diagup \overset{\parallel}{C-NH}\diagdown}}CO.$—This is found in tea and may be
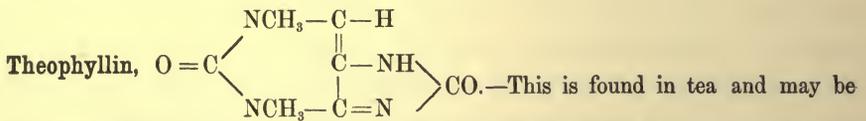
converted into caffeïn through the addition of a third methyl group.[2]

Caffeïn, Theïn, Trimethyl Xanthin, $O=C \overset{NCH_3-C-H}{\underset{NCH_3-C=N}{\diagup \overset{\parallel}{C-NCH_3}\diagdown}}CO.$
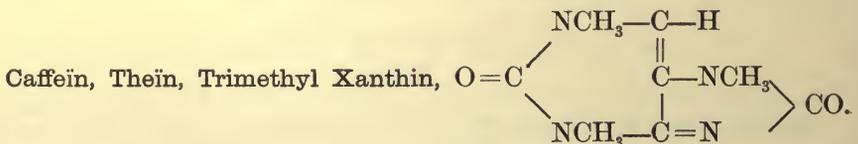
This is the alkaloid of coffee, tea, guarana, and the cola nut, imparting the nerve-stimulating properties to each. A cup of coffee contains 0.1 gram of caffeïn. If caffeïn be fed it appears in part as methyl xanthin in the urine.[3] That the compounds theobromin and caffeïn may be demethylated in the tissue is an interesting commentary on the methylation of tellurium, selenium, and pyridin by the tissues.

Guanin, Imido-xanthin, $C_5H_4N_4ONH$.—This is found, like hypoxanthin, adenin, and xanthin, in tissues rich in nuclei, and in the blood.[4] It is a decom-

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[1] Kossel : *Zeitschrift für physiologische Chemie*, 1886, Bd. 7, p. 250.

[2] *Ibid.*, 1889, Bd. 13, p. 298.

[3] Boudzynski und Gottlieb : *Archiv für exper. Pathologie und Pharmakologie*, 1895, Bd. 36, p. 45.

[4] Kossel : *Zeitschrift für physiologische Chemie*, 1884, Bd. 8, p. 404.

position product of nuclein. Combined with calcium it gives the brilliant iridescence to fish-scales.[1] It is found in the fresher layers of deposited guano, according to Voit being very probably derived from the fish eaten by the water-fowl.

(c) URIC ACIDS.

$$\text{Uric Acid, } O = C \begin{cases} NH - C = O \\ \quad\quad | \\ \quad\quad C - NH \\ \quad\quad \| \\ NH - C - NH \end{cases} > CO.$$
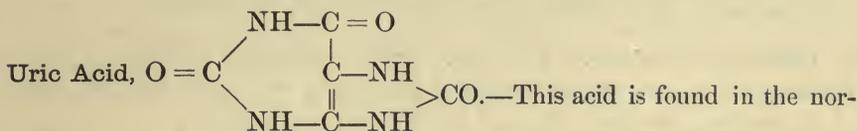
—This acid is found in the normal urine in small amounts, and may be detected in the blood and tissues, especially in gout. It is the principal excrement of birds and snakes, that of the latter being almost pure ammonium urate.

Preparation.—(1) By heating glycocoll with urea at 200° :

$$C_2H_5NO_2 + 3CO(NH_2)_2 = C_5H_4N_4O_3 + 3NH_3 + 2H_2O.$$
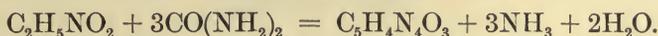
(2) By heating the amide of trichlorlactic acid with urea :

$$CCl_3CHOH.CO.NH_2 + 2CO(NH_2)_2 = C_5H_4N_4O_3 + 3HCl + NH_3 + H_2O.$$
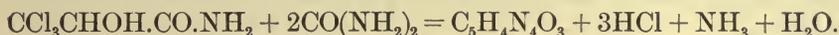
Properties.—Uric acid may be deposited in white hard crystals, which are tasteless, odorless, and almost insoluble in water, alcohol, or ether. (For its solution in the urine see p. 966.) Presence of urea adds to its solubility.[2] Its most soluble salts are those of lithium and piperazin. Uric acid is dibasic— that is, two of its hydrogen atoms may be replaced by monad elements.

(1) Nitric acid in the cold converts uric acid into urea and *alloxan :*

$$C_5H_4N_4O_3 + O + H_2O = OC \begin{matrix} NH - CO \\ NH - CO \end{matrix} CO + OC(NH_2)_2.$$

Alloxan.
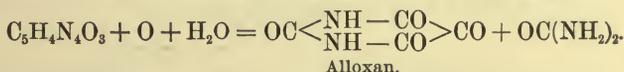
(2) Whereas, if the hot acid acts, it produces *parabanic acid :*

$$OC \begin{matrix} NH - CO \\ NH - CO \end{matrix} CO + O = OC \begin{matrix} NH - CO \\ NH - CO \end{matrix} + CO_2.$$
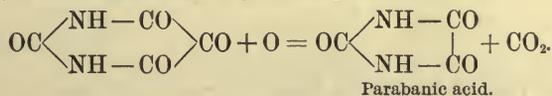
Parabanic acid.

(3) Through water addition parabanic acid becomes *oxaluric acid :*

$$OC \begin{matrix} NH - C = O \\ NH - C = O \end{matrix} + H_2O = OC \begin{matrix} NH_2 \\ NH.CO.COOH \end{matrix}$$
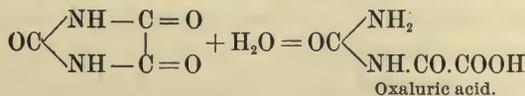
Oxaluric acid.

(4) And still another molecule of water added produces oxalic acid and urea :[3]

$$OC \begin{matrix} NH_2 \\ NH.CO.COOH \end{matrix} + H_2O = \begin{matrix} COOH \\ COOH \end{matrix} + OC(NH_2)_2.$$
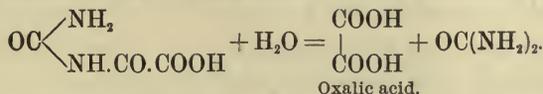
Oxalic acid.

The above reactions lead up to the constitutional formula of uric acid, and show its decomposition into urea and oxalic acid through oxidation and hydrolysis. It is known that uric acid when fed increases the amount of urea in the urine, and it is possible that the oxalic acid in the urine may have the same source.

[1] Voit : *Zeitschrift für wissenschaftliche Zoologie,* Bd. 15, p. 515.
[2] G. Rüdel : *Archiv für exper. Pathologie und Pharmakologie,* 1893, Bd. 30, p. 469.
[3] See Bunge : *Physiologische Chemie,* 1894, p. 312.

Uric acid oxidized with permanganate of potash is converted into *allantoïn*, $C_4H_6N_4O_3$, a substance which is found in the allantoic fluid, and in the urine of pregnant women and of newborn children.

If uric acid be carefully evaporated with nitric acid on a small white porcelain cover, a reddish residue remains, which moistened with ammonia gives a brilliant purple color due to the formation of *murexid*, $C_8H_4(NH_4)N_5O_6$; subsequent addition of alkali gives a red coloration. This is known as the *murexid test* and is very delicate.

Carnin, or Dimethyl Uric Acid.—The formula is unknown. Carnin is found in tissue, and has been detected in extracts of meat and in the urine.

A synthetic dimethyl uric acid of the following formula,

$$\begin{array}{c} NCH_3\text{---}C=O \\ \diagup \qquad\qquad | \\ OC \qquad\qquad C\text{---}NH \\ \diagdown \qquad\qquad \| \qquad\quad \diagdown CO, \\ NCH_3\text{---}C\text{---}NH \diagup \end{array}$$
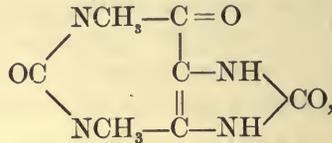
when fused with oxalic acid is converted into theophyllin.[1] This is the only transformation between the uric-acid group and the xanthin bases known in the laboratory.

THE ALLOXURIC ACIDS AND BASES IN THE BODY—To the definitely determined facts belong (1) that these substances when fed are generally converted into urea; (2) that some nucleins under proper chemical treatment break up as follows:

Nuclein.
|
┌──────────────┴──────────────┐
Proteid.　　　　　　　　　　　Nucleic acid.
　　　　　　　　　　　　　┌─────────┴─────────┐
　　　　　　Phosphoric acid.　　　　　Adenin.
　　　　　　　　　　　　　　　　　　Guanin.
　　　　　　　　　　　　　　　　　　Xanthin.
　　　　　　　　　　　　　　　　　　Hypoxanthin.
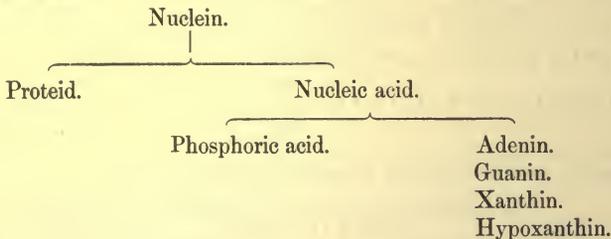
(3) that these last named substances have been obtained from no proteid other than nuclein (see Nuclein). The idea that the alloxuric bodies in mammals were metabolic products of nuclein, the uric acid being derived from oxidation of the bases, was especially emphasized by Horbaczewski.[2] His statement that uric acid and the bases are increased in the urine after feeding nuclein has been confirmed.[3] The increase of alloxuric bodies in the urine in leucocythæmia has long been known, and is now explained by the increased nuclein-metabolism following the destruction of the white blood-corpuscles. An interesting investigation of a case of leucocythæmia [4] has shown that ingested theobromin is burned as in the normal person; the explanation is offered that the alloxuric bodies produced

[1] Fischer and Acht: *Berichte der Berliner Academie*, 1895, p. 259.

[2] *Sitzungsberichte der Wiener Akademie den Wissenschaften*, 1891, Bd. C. Abth. iii. p. 13.

[3] Weintraud: Verhandlung der Berliner physiologische Gesellschaft, *Archiv für Physiologie*, 1895, p. 382.

[4] Boudzynski and Gottlieb: *Archiv für exper. Pathologie und Pharmakologie*, 1895, Bd. 36, p. 127.

in the body in some way have lesser opportunities for oxidation than those introduced into it. Experiments on this same case have shown that, though the proportion of daily uric-acid nitrogen to total nitrogen in the urine may vary considerably (1 : 63 to 1 : 88), the proportion of the nitrogen of uric acid plus the bases to total nitrogen is quite constant (1 : 48.3 to 1 : 40.8) ; from this may be inferred that there is greater or less production of uric acid through oxidation of the bases on different days. This may be interpreted as affording the missing link in explanation of the conversion of the bases into uric acid. If xanthin itself be fed, it is not converted into uric acid. According to Horbaczewski,[1] uric acid is produced from nuclein by digesting putrid extract of the spleen with blood.

Xanthin fed to birds is converted into uric acid. In birds the formation of uric acid depends on a synthetic union of ammonia and lactic acid in the liver, since on extirpation of the liver the last two substances appear in the urine in amounts proportional to the normally formed uric acid (see p. 989).

The literature on the subject of gout is enormous. It is sufficient to remark here that it is not even known whether gout is due to an increased formation or an increased retention of uric acid. The amount of uric acid in the blood is certainly increased. The normal amount of uric acid in the daily urine is put at 0.7 gram, that of the alloxuric bases at 0.1325.[2] The amount of the bases may be quadrupled in leucocythæmia.[3] Whether all the alloxuric bodies produced in the organism are eliminated, or whether they are partially burned, is a matter of controversy.

Diatomic Dibasic Acids, $C_nH_{2n-2}O_4$.

Oxalic Acid, $\begin{matrix} COOH \\ | \\ COOH \end{matrix}$.—This is found as calcium oxalate in the urine, and is present in most plants. Its possible origin from uric acid has been mentioned. It is a product of boiling proteid with barium hydrate. It may be obtained synthetically by heating sodium formate :

$$2HCOONa = \begin{matrix} COONa \\ | \\ COONa \end{matrix} + 2H.$$
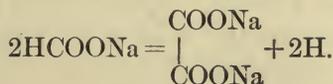
Oxalic acid and its alkaline salts are very soluble in water. Its calcium salts are insoluble in water and dilute acetic acid, but are soluble in the acid phosphates of the urine.

If oxalic acid be given subcutaneously it appears unchanged in the urine.[4] Given *per os* it undoubtedly unites with the calcium salts of the gastric and other juices, and is therefore but partially absorbed. After feeding a man with meat alone, or with meat, fat, and sugar, Bunge[5] could find no oxalates

[1] *Loc. cit.*   [2] Krüger and Wulff: *Zeitschrift für physiologische Chemie*, 1895, Bd. 20, p. 184.
[3] Boudzynski and Gottlieb, *Op. cit.*, p. 132.
[4] Gaglia: *Archiv für exper. Pathologie und Pharmakologie*, 1887, Bd. 22, p. 246.
[5] *Physiologische Chemie*, 1894, p. 340.

in the urine. He therefore concludes that the oxalic acid in the urine is derived from the oxalates of the food and not from metabolism in the body. Stones in the bladder are sometimes composed of calcium oxalate, as are also urinary sediments when formed in consequence of ammoniacal fermentation.

Succinic Acid, $HOOC.C_2H_4.COOH$.—This has been detected in the spleen, thymus, thyroid, in echinococcus fluid, and often in hydrocele fluid. It is a product of alcoholic fermentation, and of proteid putrefaction. It is often found in plants.

Amido-succinic Acid, or Aspartic Acid, $HOOC.C_2H_3NH_2.COOH$. This is a product of boiling proteid with acid or alkalies, and it is also formed under the influence of trypsin in proteid digestion.

Monamide of Amido-succinic Acid, or Asparagin, $H_2NOC.C_2H_3NH_2.COOH$. —This is found widely distributed in plants, especially in the germinating seed. If a plant be placed in the dark its proteid nitrogen decreases, whereas the non-proteid nitrogen increases,[1] the cause of this being attributed to proteid metabolism with the production of amido- acids, *i. e.* aspartic and glutamic acids, leucin, and tyrosin. In the sunlight, it is believed, these bodies are later reconverted into proteid. One view regarding the for- mation of asparagin is based theoretically on the production of succinic acid from carbo- hydrates (as in alcoholic fermentation) and the subsequent formation of *oxysuccinic acid* (or *malic acid*, $HOOC.C_2H_3OH.COOH$), which the inorganic nitrogenous salts change to asparagin.[2] At any rate asparagin in the plant has the power of being constructed into proteid. Since proteid in the animal body may yield 45 per cent. of dextrose in its decomposition, as will be shown, it seems fair to surmise that the synthesis of proteid in the plant may in part depend upon the union of asparagin or similar amido- compounds with the carbohydrates present. Asparagin if fed is converted into urea. It forms no proteid synthesis in the animal, and has only a very small effect as a food-stuff.[3]

Glutamic acid, $HOOC.CHNH_2.CH_2.CH_2.COOH$.—This is found as a cleavage- product of tryptic digestion in the intestinal canal. *Glutamin*, its amido- compound, is, like asparagin, widely distributed in the vegetable kingdom and in considerable amounts. It probably plays the same rôle as asparagin in the plant. Glutamin is more soluble than asparagin and is therefore less easily detected.

Compounds of Triatomic Alcohol Radicals.

Glycerin, or Propenyl Alcohol, $CH_2OH.CHOH.CH_2OH$. The glycerin esters of the fatty acids form the basis of all animal and vegetable fats. Glycerin is furthermore formed in small quantities in alcoholic fermentation.

Preparation.—(1) Through the action of an alkali on a fat, glycerin and a *soap* are formed, a process called *saponification:*

$$2C_3H_5(C_{18}H_{35}O_2)_3 + 6NaOH = 2C_3H_5(OH)_3 + 6NaC_{18}H_{35}O_2.$$
Stearin.   Sodium stearate.
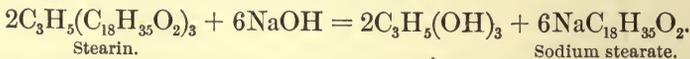
(2) Fats may be decomposed into glycerin and fatty acid by superheated steam, and likewise by the fat-splitting ferment in the pancreatic juice. Thus, if a thoroughly washed butter-ball, consisting of pure neutral fat, be colored with blue litmus, and a drop of pancreatic juice be placed upon it, the mass

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[1] Schulze and Kisser: *Landwirthschatfliche Versuchs-Station*, 1889, Bd. 36, p. 1.

[2] Müller: *Ibid.*, 1886, Bd. 33, p. 326.

[3] See Voit: *Zeitschrift für Biologie*, 1892, Bd. 29, p. 125.

will gradually grow red in virtue of the fatty acid liberated from its glycerin combination. This reaction takes place to some extent in the intestine.

If fatty acid be fed, the chyle in the thoracic duct is found to contain much neutral fat.[1] This synthesis indicates the presence of glycerin in the body—perhaps, in this case, in the villus of the intestine: the source of this glycerin, whether from proteid or carbohydrates, is problematical. If glycerin be fed, only little is absorbed (since diarrhœa ensues), and of that little some appears in the urine. In its pure form, therefore, it seems to be oxidized with difficulty in the body.

Glycerin Aldehyde, $HOCH_2.CHOH.CHO$, and **Dioxyacetone**, $HOCH_2.CO.CH_2OH$.—These substances are formed by the careful oxidation of glycerin with nitric acid, and together are termed *glycerose*. They have a sweet taste and are the lowest known members of the glycose (sugar) series—*i. e.* substances which are characterized by the presence of either aldehyde-alcohol, —CHOH—CHO, or ketone-alcohol, —CO—CH$_2$OH, radicals. The constituents of glycerose, from the number of their carbon atoms, are called *trioses*. On boiling glycerose with barium hydrate the two constituents readily unite to form *i*-fructose (levulose).

Glycerin Phosphoric Acid, $(HO)_2C_3H_5.H_2PO_4$.—This is the only ethereal phosphoric acid in the urine. It is found in mere traces, its source being the lecithin decomposed in the body.[2]

Lecithin, $C_3H_5 {{/\!/(C_nH_{2n-1}O_2)_2} \atop {\backslash O.PO.(OH).O.C_2H_4.N(CH_3)_3OH}}$.—Lecithin is found in every cell, animal or vegetable, and especially in the brain and nerves. It is found in egg-yolk, in muscles, in blood-corpuscles, in lymph, pus-cells, in bile, and in milk. On boiling lecithin with acids or alkalies, or through putrefaction in the intestinal canal, it breaks up into its constituents, fatty acids, glycerin phosphoric acid, and cholin (see p. 986), substances which the intestine may absorb. The fatty acids may be stearic, palmitic, or oleic, two molecules of different fatty acids sometimes uniting in one molecule of lecithin: hence there are varieties of lecithins. Through further putrefaction cholin breaks up into carbonic oxide, methane, and ammonia.[3] Lecithin treated with distilled water swells, furnishing the reason for the " myelin forms" of nervous tissue. Lecithin is readily soluble in alcohol and ether. It feels waxy to the touch. *Protagon*, which has been obtained especially from the brain, is a crystalline body containing lecithin and *cerebrin*—which is a glucoside (a body separable into proteid and a sugar). The chemical identity of protagon is shown in that ether and alcohol will not extract lecithin from it.[4] Protagon readily breaks up into its constituents. While protagon seems to be regarded as the principal form in which lecithin occurs in the brain, simple lecithin is believed to be present in the nerves and other organs. This subject has not been properly worked out. Regarding the synthesis of

[1] Munk: *Virchow's Archiv*, 1880, Bd. 80, p. 17.
[2] Sotnitschewsky: *Zeitschrift für physiologische Chemie*, 1880, Bd. 4, p. 214.
[3] Hasebroek: *Ibid.*, 1888, Bd. 12, p. 148.
[4] Gamgee and Blankenhorn: *Journal of Physiology*, 1881, vol. ii. p. 113.

lecithin in the body, or the physiological importance of the substance, absolutely nothing is known.

FAT IN THE BODY.—Animal and vegetable fats consist principally of a mixture of the triglycerides of palmitic, stearic, and oleic acids. In the intestines the fat-splitting ferments convert a small portion of fat into glycerin and fatty acid; the fatty acid unites with alkali to form a soap, in the presence of which the fat breaks up into fine globules called an *emulsion;* if now the fine globules and the intestinal wall be wet with bile, fat is absorbed, and may be burned in the cells or deposited in the adipose tissue.

Fat may likewise be derived from ingested carbohydrates. The chemical derivation of fatty acid from carbohydrates has already been mentioned in the case of formic, acetic, propionic (see p. 980), and butyric acids. The fatty acids of fusel oils are likewise formed from carbohydrates in fermentation. The laboratory synthesis of sugar from glycerin has been already related. These reactions, however, furnish only the smallest indication of the large transformation of carbohydrates into fat possible in the body.

If geese be fed with rice in large quantity, and the excreta and air respired be analyzed, it may be shown that carbon is retained in large amount by the body, in amount too great to be entirely due to the formation of glycogen, and must therefore have been deposited in the form of fat.[1] Such fattening of geese produces the delicate *pâté de foie gras.* The principle has been established in the case of the dog as well.[2]

The formation of fat from proteid (fatty degeneration) has been established with all certainty in pathological cases (see p. 957). Recollection of the fact that proteid may yield 45 per cent. of sugar aids in the comprehension of this problem.

Other usually cited proofs of the formation of fat from proteid include the conversion of casein into fat incident to the ripening of cheese; and the transformation of muscle in a damp locality into a cheese-like mass called *adipocere,* which is probably effected by bacteria.[3] Adipocere contains double the original quantity of fatty acid, occurring as calcium, and sometimes as ammonium salts.

Experiments of C. Voit show that on feeding large quantities of proteid, not all the carbonic acid is expired that belongs to the proteid destroyed as indicated by the nitrogen in the urine and feces. The conclusion follows that a non-nitrogenous substance has been stored in the body. Too much carbon is retained to be present only in the form of glycogen; fat from proteid must therefore have been stored.[4] The formation of fat normally from proteid has been violently combated by Pflüger, it would seem without proper foundation. For behavior of fat in the cell see p. 999.

Oleic Acid, $C_{18}H_{34}O_2$.—This acid belongs to the series of fatty acids having the formula $C_nH_{2n-2}O_2$. Its glyceride solidifies only as low as $+4°$ C. It is the principal compound of liquid oils. Pure stearin is solid at the body's temperature, but mixed with oleïn the melting-point of the mixture is reduced below the temperature of the body and its absorption is thereby rendered possible. The fat in the body is all in a fluid condition, due to the presence of oleïn.

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[1] Voit: Abstract in *Jahresbericht über Thierchemie,* 1885, Bd. 15, p. 51.

[2] Rübner : *Zeitschrift für Biologie,* 1886, Bd. 22, p. 272.

[3] Read Lehmann: Abstract in *Jahresbericht über Thierchemie,* 1889, Bd. 19, p. 516.

[4] Erwin Voit: *Münchener medicinische Wochenschrift,* No. 26, 1892; abstract in *Jahresbericht über Thierchemie,* 1892, p. 34.

CARBOHYDRATES.

The important sugar of the blood and the tissues is dextrose. It is derived from the hydration of starchy foods, and from proteid metabolism. From dextrose the lactic glands manufacture another carbohydrate, milk-sugar. Cane-sugar forms an article highly prized as a food. The study of the various sugars or carbohydrates is of especial interest because their chemical nature is now well known.

Carbohydrates were formerly defined as bodies which, like the sugars and substances of allied constitution, contain carbon, hydrogen, and oxygen, the carbon atoms being present to the number of six or multiples thereof, the hydrogen and oxygen being present in a proportion to form water. *Glycoses* include the monosaccharides like dextrose, $C_6H_{12}O_6$; *disaccharides* include, for example, cane-sugar, $C_{12}H_{22}O_{11}$, which breaks up into dextrose and levulose, while *polysaccharides* comprise such bodies as starch and dextrins, which have the formula $(C_6H_{10}O_5)_n$.

In recent years the term glycose has been extended to cover bodies having three to nine carbon atoms and possessing either the constitution of an aldehyde-alcohol, —CH(OH)CHO, called *aldoses*, or of a ketone-alcohol, —COCH₂OH, called *ketoses*. These bodies also have hydrogen and oxygen present in a proportion to form water, and the number of carbon atoms always equals in number those of oxygen. According to their number of carbon atoms they are termed trioses, tetroses, pentoses, hexoses, heptoses, octoses, and nonoses.

It has been shown (foot-note, p. 989) how from the asymmetric carbon atom in lactic acid two configurations are derived. If a body (such as trioxybutyric acid) contains two asymmetric carbon atoms, four configurations are possible,

$$\begin{array}{cccc}
CH_2OH & CH_2OH & CH_2OH & CH_2OH \\
HCOH & OHCH & OHCH & HCOH \\
HCOH & OHCH & HCOH & OHCH \\
COOH & COOH & COOH & COOH \\
\end{array}$$
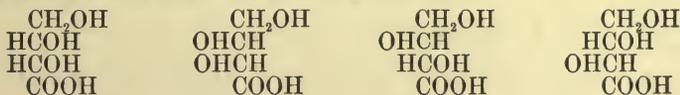
Similarly among the glycose-aldoses, a triose has two modifications; a tetrose, four; a pentose, eight: a hexose, sixteen, etc. Thus in the following formula by the variations of H and OH on the four asymmetric carbon atoms, sixteen possible hexoses may be obtained.

$$\begin{array}{c}
CH_2OH \\
-C- \\
-C- \\
-C- \\
-C- \\
CHO \\
\end{array}$$
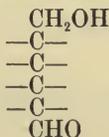
The carbohydrates have well-defined optical properties, rotating polarized light to the right or left, and are therefore designated as *d-* (dextro-) and *l-* (lævo-) respectively. An inactive (*i-*) form consists in an equal mixture of the two others. Where the OH group is attached on the right it may be indicated by the sign +, on the left by —, or the + OH may be written below, the — OH above.

$$\begin{array}{ll}
CHO & CHO \\
HCOH & C+ \\
OHCH & C- \\
HCOH & C+ \\
HOCH & C+ \\
CH_2OH & CH_2OH \\
\end{array}$$

$$\text{or } CH_2OH \begin{array}{cccc} H & H & OH & H \\ C & C & C & C \\ OH & OH & H & OH \end{array} CHO$$

d-Glucose.
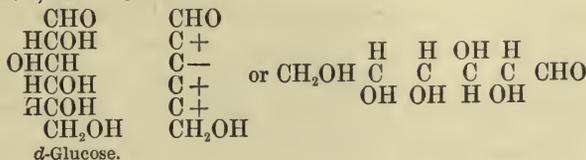
The Glycoses.

The triose called glycerose has already been described.

A tetrose called *erythrose*, which is the aldose of erythrite, $C_4H_6(OH)_4$, a tetratomic alcohol, is known.

Of the possible pentoses, *arabinose*, *xylose*, and *rhamnose* (methyl-arabinose) occur in the vegetable kingdoms in considerable quantity. They may be absorbed by the intestinal canal.[1]

Hexoses, or Glucoses.—Through the oxidation of hexatomic alcohols there may be obtained, first, glucoses, then monocarbonic acids, and lastly saccharic acid, or its isomer mucic acid:

$$C_5H_6(OH)_5CH_2OH. \qquad C_5H_6(OH)_5CHO. \qquad C_5H_6(OH)_5COOH.$$

<div align="center">Mannite.   Mannose   Mannonic acid.
(and levulose).</div>

$$C_5H_6(OH)_4(COOH)_2.$$

<div align="center">Saccharic acid.</div>
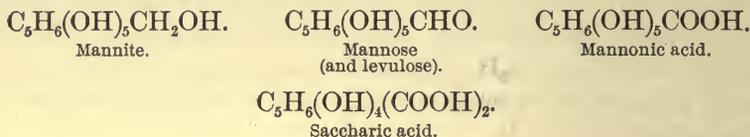
Mannose and *levulose* are respectively the aldose and ketose of mannite, *galactose* is the aldose of dulcite, whereas *glucose* is probably the aldose of sorbite—dulcite and sorbite being, like mannite, hexatomic alcohols.

Properties.—(1) The hexoses are converted into their respective alcohols on reduction with sodium amalgam.

(2) The hexoses act as reducing agents, converting alkaline solutions of cuprous oxide salts (obtained through presence of tartrate) into red cuprous oxide, which precipitates out (Trommer's test). Levulic acid is among the products formed (see p. 982). Of the higher saccharides only maltose and milk-sugar give this reaction.

(3) Strongly characteristic are the insoluble crystalline compounds formed by all glycoses with phenylhydrazin, called *osazones* (see p. 977):

$$C_6H_{12}O_6 + 2H_2N.NH(C_6H_5) = C_6H_{10}O_4(:N.NH.C_6H_5)_2 + 2H_2O + H_2.$$

<div align="center">Levulose.   Phenylhydrazin.   Glycosazone.</div>

Levulose, dextrose, and mannose give the same glycosazone. The glycosazones are decomposed into osones by fuming hydrochloric acid:

$$C_6H_{10}O_4(:N.NH.C_6H_5)_2 + 2H_2O = C_6H_{10}O_6 + 2H_2N.NH.C_6H_5.$$

<div align="center">Glycosone.</div>
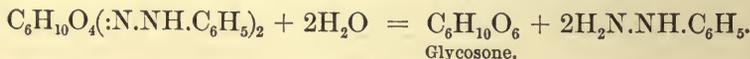
Osones are converted into sugar by nascent hydrogen. The osone derived from levulose, dextrose, and mannose yields levulose by this treatment, and the transformation of dextrose and mannose into levulose is therefore demonstrated.

(4) Only trioses, hexoses, and nonoses are capable of alcoholic fermentation.

Synthesis of the Glucoses.—Formose may be purified by means of phenylhydrazin as above, so that pure *i*-fructose is obtained; this treated with sodium amalgam yields *i*-mannite, which on oxidation is converted into *i*-mannonic acid; this last is separated by a strychnin salt into its two components; the

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[1] Weiske: *Zeitschrift für physiologische Chemie*, 1895, Bd. 20, p. 489.

d-mannonic acid is divided and one part treated with hydrogen, with resulting d-mannose, which, as has been shown above, is convertible into d-fructose or ordinary fruit-sugar; the second part of the d-mannonic acid treated with chinolin is transformed through change in configuration into its isomer, d-gluconic acid, which on reduction yields d-glucose, or ordinary dextrose. This shows the preparation of the common sugars from their elements. The transformation of levulose into dextrose is especially to be noted, since it takes place in the body.

$$d\text{-Glucose, Dextrose, Grape-sugar, } CH_2OH \overset{H}{\underset{OH}{C}} \overset{H}{\underset{OH}{C}} \overset{OH}{\underset{H}{C}} \overset{H}{\underset{OH}{C}} CHO.—$$
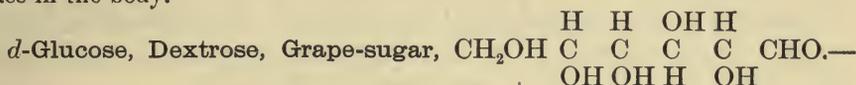
This is the sugar of the body. It is found in the blood and other fluids and in the tissues to the extent of 0.1 per cent. and more, even during starvation. The principal source of the dextrose of the blood is that derived from the digestion of starch, and also of cane-sugar, in the intestinal tract. Dextrose is likewise produced from proteid, for a diabetic patient fed solely on proteid may still excrete sugar in the urine. Minkowski[1] finds that in starving dogs after extirpation of the pancreas the proportion of sugar to nitrogen is 2.8 : 1. The same ratio has been shown to exist in phlorizin diabetes in rabbits[2] when the drug is administered in a certain way.

In calculating this production of glucose from proteid, it is discovered to be a process of oxidation, in which 45 grams of dextrose are formed from every 100 grams of proteid decomposed.[3] The sugar so formed contains 44 per cent. of the physiologically available energy of the proteid consumed. The pancreas may perhaps manufacture a ferment which, supplied to the tissues, becomes the first cause of the decomposition of dextrose, and in whose absence diabetes ensues. Excess of dextrose in the body is stored up, especially in the liver-cells, as *glycogen*, which is the anhydride of dextrose; the glycogen may be afterwards reconverted into dextrose. The presence of sugar in the body in starvation, even when little urea may be detected there, shows the readier excretion of the nitrogenous radical of proteid. Traces of dextrose are found in normal urine.

Dextrose is a sweet-tasting crystalline substance; its solutions rotate polarized light to the right.

$$d\text{-Fructose, Levulose, Fruit-sugar, } CH_2OH \overset{H}{\underset{OH}{C}} \overset{H}{\underset{OH}{C}} \overset{OH}{\underset{H}{C}} COCH_2OH.—$$
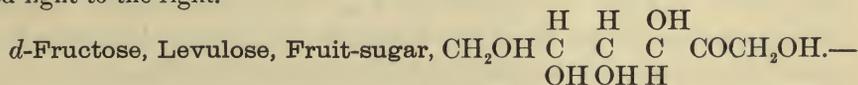
This occurs in many fruits and in honey. It is sweeter than dextrose, and rotates polarized light to the left. It is a product of the decomposition of cane-sugar in the intestinal canal. If levulose be fed, any excess in the blood may be converted into glycogen, and through the glycogen into dextrose. It is possible thus to convert 50 per cent. of the levulose fed into dextrose.[4]

[1] *Archiv für Physiologie und Pharmakologie,* 1893, Bd. 31, p. 85.
[2] Lusk: Paper read before the American Society of Physiology, Philadelphia, 1895.
[3] Weintraud and Laues: *Zeitschrift für physiologische Chemie,* 1894, Bd. 19, p. 632.
[4] Minkowski: *Archiv für Pathologie und Pharmakologie,* 1893, Bd. 31, p. 157.

When levulose is fed to a diabetic patient, it may be burned, though power to burn dextrose has been lost.[1]

$$d\text{-Galactose, } CH_2OH \quad \overset{H}{\underset{OH}{C}} \quad \overset{OH}{\underset{H}{C}} \quad \overset{OH}{\underset{H}{C}} \quad \overset{H}{\underset{OH}{C}} \quad CHO.$$—This is found combined
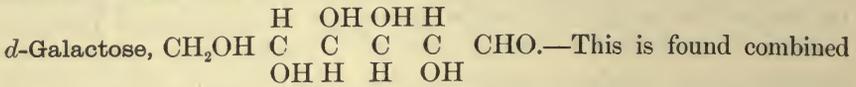
with proteid in the brain, forming the glucoside cerebrin. It is produced together with dextrose in the hydrolytic decomposition of milk-sugar. It does not undergo alcoholic fermentation, at least not with *Saccharomyces apiculatus*. When fed it is not converted directly into glycogen, but through its burning it spares the decomposition of some of the dextrose produced from proteid, which latter may of course be converted into glycogen.[2]

THE DISACCHARIDES, $C_{12}H_{22}O_{11}$.

These are di-multiple sugars in ether-like combination. To cane-sugar and milk-sugar, Fisher has ascribed the following formulæ :[3]

CANE-SUGAR.

```
  CH——       CH₂OH
 /CHOH    O\  C
O  CHOH     /CHOH
 \CH     O/  CHOH
  CHOH      \CH
  CH₂OH       CH₂OH
```
Dextrose group.   Levulose group.

MILK-SUGAR.

```
 CH₃OH      CHO
 CHOH       CHOH
 CH         CHOH
/CHOH       CHOH
O\CHOH      CHOH
 CH    —O—  CH₂
```
Galactose group.   Dextrose group.
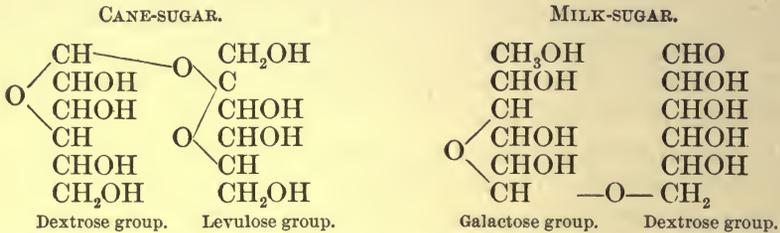
Cane-sugar, or Saccharose.—Cane-sugar, obtained from the sugar-cane and the beet-root, is largely used to flavor the food, and likewise assumes importance as a food-stuff. On boiling with dilute acids, cane-sugar is converted through hydrolysis into a mixture of levulose and dextrose. The same result is obtained by warming with 0.2 per cent. hydrochloric acid at the temperature of the body. This inversion, therefore, takes place in the stomach. In the intestinal canal the inversion is accomplished through the action of a ferment present in the intestinal juice. Subcutaneous injection of cane-sugar shows that it is not directly converted into glycogen, but that in burning it spares some dextrose coming from proteid decomposition, and this latter is converted into glycogen and may be found in the liver and muscles. But fed *per os*, cane-sugar is the cause of a large glycogen storage, in virtue of its greater or less conversion into dextrose and levulose in the intestines.

Milk-sugar, or Lactose.—This is found in the milk and in the amniotic fluid. It is probably manufactured from dextrose in the mammary glands, for the blood does not contain it. It is sometimes present in the urine during the last days of pregnancy, and almost always during the first days of lactation. It readily undergoes lactic fermentation, producing lactic acid, which then causes clotting of the milk. This fermentation may take place in the intestinal tract. Boiling with dilute acids splits up milk-sugar into galactose and dextrose.

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[1] *Loc cit.*   [2] C. Voit: *Zeitschrift für Biologie,* 1891, Bd. 28, p. 245.
[3] *Berichte der deutschen chemischen Gesellschaft,* 1894, Bd. 26, p. 2400.

This decomposition probably does not take place in the stomach. Neither does the intestinal juice cause this transformation.[1] Milk-sugar is probably absorbed unchanged, and is not a glycogen-producer except indirectly in the sense of sparing proteid dextrose which may become glycogen.[2] The contrary view, *i. e.* that milk-sugar is converted into dextrose and galactose, is held by Minkowski[3] and others. The question is not definitely settled.

Isomaltose.—This is the only disaccharide which has been synthetically obtained, having been produced by boiling dextrose with hydrochloric acid. It ferments with difficulty and forms an osazone which melts at 150°–153°. It, with dextrin, is a product of the action of diastase and of the diastatic enzymes found in saliva, pancreatic juice, intestinal juice, and blood upon starch and glycogen. Through further action of the same ferments isomaltose is converted into maltose.

Maltose.—Maltose (and dextrin) are the end-products of the action of diastase on starch and glycogen, the process being one of hydrolysis:

$$3C_6H_{10}O_5 + H_2O = \underset{\text{Maltose.}}{C_{12}H_{22}O_{11}} + \underset{\text{Dextrin.}}{C_6H_{10}O_5}.$$
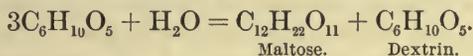
It is likewise a product of the diastatic action of ptyalin (saliva), amylopsin (pancreatic juice), and of ferments in the intestinal juice and in the blood. Maltose readily undergoes alcoholic fermentation and forms an osazone which melts at 206°. It is converted into dextrose by boiling with acids. Certain ferments convert maltose (and dextrin) into dextrose (see Starch).

CELLULOSE GROUP, $(C_6H_{10}O_5)_n$.

Cellulose.—This is a highly polymerized anhydride of dextrose, perhaps also of mannose. It forms the cell-wall in the plant. It undergoes putrefaction in the intestinal canal, especially in herbivora (see p. 976), and owing to the production of fatty acids it may have value as a food. In man only young and tender cellulose is digested, such as occurs in lettuce and celery. The bulk of herbivorous fecal matter consists of cellulose. Cellulose is only with difficulty attacked by acids and alkalies. Tunicin, found among the tunicates, is identical with cellulose, so that the substance is not solely characteristic of the vegetable kingdom.

Starch, $(C_6H_{10}O_5)_{20}$.—This substance on boiling with dilute acids breaks down by hydrolysis principally to dextrose. It is found in plants, and may be manufactured by them from cane-sugar, dextrose, levulose, and from other sugars. It forms a reserve food-stuff, being converted into sugar as the plant requires it—in winter, for example. Starch gives a blue color with iodine. According to recent investigations[4] starch is said to be broken up by diastase into five successive hydrolytic cleavage-products as follows: (1) *Amylodextrin* $(C_{22}H_{20}O_{10})_{54}$, a substance giving a deep-blue color with iodine. This is next changed to (2) *Erythrodextrin,* $(C_{12}H_{20}O_{10})_{18} + H_2O$, or $(C_{12}H_{20}O_{10})_{17}$.

[1] Pregl: *Pflüger's Archiv,* 1895, Bd. 61, p. 359.   [2] C. Voit, *Op. cit.,* p. 260 *et seq.*

[3] *Archiv für exper. Pathologie und Pharmakologie,* 1893, Bd. 31, p. 161; Kausch and Socin, *ibid.,* 1893, Bd. 31, p. 398.

[4] Lintner and Düll: *Berichte der deutschen chemischen Gesellschaft,* 1893, Bd. 26, p. 2533.

($C_{12}H_{22}O_{11}$), which is readily soluble in water and gives with iodine a reddish-brown color. Erythrodextrin is converted into (3) *Achroodextrin*, $(C_{12}H_{20}O_{10})_6$ $+ H_2O$, or $(C_{12}H_{20}O_{10})_5.C_{12}H_{22}O_{11}$, which is likewise very soluble, tastes slightly sweet, but gives no coloration with iodine. Achroodextrin now breaks up into (4) *Isomaltose*, which through change in configuration is transformed to its isomere (5) *Maltose*.

Products similar to these are formed by the various diastatic ferments in the body, and in addition also some dextrose. Ptyalin[1] acts rapidly on starch, producing dextrin and maltose, but very little dextrose. Amylopsin, from the pancreas, acts still more rapidly than ptyalin, and with the production of considerable dextrose. The diastatic ferment of intestinal juice acts very slowly on starch, forming dextrin, maltose, and a little dextrose, while the ferment in blood-serum likewise acts slowly but with complete transformation of all the maltose and dextrin formed, into dextrose.

The above facts lead Hamburger to suggest that the diastatic ferments of the body consist of mixtures, in different proportions, of diastase, which forms dextrin and maltose from starch, and of glucase, which converts these into dextrose. This, however, is merely an hypothesis, and glucase has never been prepared. The vegetable diastase is not identical with that found in the body. Thus ptyalin, like emulsin, breaks up salicin into salicylic alcohol and dextrose, of which action vegetable diastase is incapable. But ptyalin, again, is not identical with emulsin, for it will not act on amygdalin.

Glycogen, or Animal Starch.—Recent investigations have shown that in all the particulars of diastatic decomposition glycogen is identical with vegetable starch.[2] Glycogen is soluble in water, giving an opalescent fluid. The blood has a normal composition which does not greatly vary. After a hearty meal excess of fat is deposited in fatty tissue, excess of proteid in the muscular tissue, while excess of sugar is stored in the muscles and especially in the liver-cells in the less combustible and less diffusible form of glycogen. About one-half of the total quantity of glycogen is found in the muscles, the remainder in the liver, where it may even amount to 40 per cent. of the dry solids. When the blood becomes poor in sugar, the store of glycogen is drawn upon to such an extent that in hunger the body becomes glycogen-free. Muscular work likewise causes the rapid conversion of glycogen into sugar. The sources of glycogen are certain ingested carbohydrates, and also the dextrose derived from proteid. If large quantities of proteid be fed, glycogen may be stored. If milk-sugar and galactose be burned in the cells of an otherwise starving animal, the dextrose from proteid is economized and glycogen is found. If dextrose or levulose (or anything which produces dextrose, *e. g.* cane-sugar, maltose) be fed, there is a direct conversion of the sugar into glycogen. Voit[3] has called attention to the fact that only directly fermentable sugars are convertible into glycogen. Cremer[4] shows that yeast-cells contain much glycogen when cultivated in media which they ferment, not, however, when cultivated in milk-

[1] See Hamburger: *Pflüger's Archiv*, 1895, Bd. 60, p. 573.
[2] Külz and Vogel: *Zeitschrift für Biologie*, 1895, Bd. 31, p. 108.
[3] *Zeitschrift für Biologie*, 1891, Bd. 28, p. 270.
[4] *Ibid.*, 1895, Bd. 31, p. 188.

sugar, for example. So perhaps, in levulose-fermentation the first step may be conversion into glycogen or the anhydride of dextrose. Cremer maintains that the pentoses are burned in the body, but are only indirectly glycogen-producers.

Dextrins.—These have been described under starch.

d**-Glucuronic Acid, or Glycuronic Acid,** $HOOC\overset{H}{\underset{OH}{C}}\ \overset{H}{\underset{OH}{C}}\ \overset{OH}{\underset{H}{C}}\ \overset{H}{\underset{OH}{C}}\ CHO.$

—Obtained by reducing d-saccharic acid with nascent hydrogen. After feeding chloral hydrate, naphthalin, camphor, terpentine, phenol, ortho-nitrotoluol, and other bodies, they appear in the urine (usually having been first converted into alcohol) in combination with glycuronic acid. Urochloralic acid, naphthol-glycuronic acid, campho-glycuronic acid, terpene-glycuronic acid, etc., all rotate polarized light to the left. It seems that these ingested substances unite in the body with the aldehyde group of dextrose, at the same time protecting all but one group of the dextrose molecule from further oxidation (Fischer). Glycuronic acid, which is easily separated by hydrolysis from its aromatic combination, itself rotates polarized light to the right, reduces alkaline copper solutions, and might be confounded with dextrose except that it does not ferment with yeast. Glycuronic acid is likewise found in the urine after administration of curare, morphine, and after chloroform-narcosis, perhaps paired with aromatic bodies formed in the organization.

COMBUSTION IN THE CELL IN GENERAL.—Experiments[1] show that taking the proteid decomposition in the starving dog as 1, it is necessary to feed three to four times that amount of proteid taken alone in order to attain nitrogenous equilibrium, 1.6 to 2.1 times that amount of proteid when fed with fat, and 1 to 1.2 times that amount when fed with carbohydrates. The physiological proteid minimum is in these cases never less than the amount required in starvation. Only after feeding gelatin with proteid may the proteid fed be below the amount decomposed in starvation. The above shows what is well known, that sugar spares proteid from decomposition more than fat does. E. Voit[2] states these two propositions: (1) The part played by these several food-stuffs in the total metabolism depends on the composition of the fluid feeding the cell. The greater the amount of one of these food-stuffs, the greater its decomposition and the less the decomposition of the others, so long as the total decomposition suffers no change. (2) The several food-stuffs do not act wholly on account of their quantity in the fluid surrounding the cell, but especially according to the chemical affinity of the cell-substance for them individually. First in this regard comes proteid, then carbohydrates, and lastly fat.

The excessive proteid decomposition in diabetes is due to the non-combustion of the proteid protecting sugars[3] and the same is true in fever where a small supply of carbohydrates reaches the blood.[4]

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[1] E. Voit and Korkunoff: *Zeitschrift für Biologie*, 1895, Bd. 32, p. 117.
[2] *Op. cit.*, pp. 128 and 135.   [3] Lusk: *Zeitschrift für Biologie*, 1890, Bd. 27, p. 459.
[4] May: *Ibid.*, 1894, Bd. 30, p. 1.

For further discussion of carbohydrates in the body see under the individual sugars, and under Fat in the Body.

BENZOL DERIVATIVES OR AROMATIC COMPOUNDS.

The aromatic compounds are characterized by a configuration in which six atoms of carbon are linked together in a circle called the benzol ring. The type of this is benzol, a hydrocarbon found in coal-tar and having the formula,
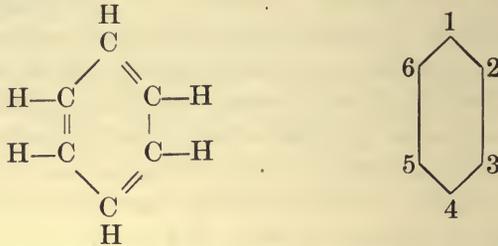
The hydrogen atoms may be substituted for others, substitution of one OH group, for example, forming phenol, C_6H_5—OH. If, however, two OH groups are substituted, three different bodies, corresponding to the different arrangements on the ring, become possible. If the two OH groups occupy the positions 1 and 2 the substance is *ortho*-dioxybenzol; if 1 and 3, *meta*-dioxybenzol; and if 1 and 4, *para*-dioxybenzol.

It is possible to convert bodies of the fatty series into those of the aromatic. Acetylene passed through red-hot tubes yields benzol. On the other hand, aromatic bodies may be converted into those of the fatty series. If phenol in aqueous solution be subjected to electrolysis by an alternating current under which circumstances hydrogen and oxygen are alternately liberated on the same pole, the effect of this intermittent oxidation and reduction is to break up the phenol into caproic acid, and finally, after passing through acids of lower carbon contents, into carbonic acid and water.

The aromatic compounds found in the urine are normally exclusively derived from the products of proteid putrefaction in the intestines. It is admitted that neither fats nor carbohydrates play any part in their formation.

Benzol, C_6H_6.—This body if fed is absorbed and afterward converted into oxybenzol or phenol, with subsequent behavior similar to phenol.

Phenol (Carbolic Acid, Oxybenzol, Phenyl-hydroxide), C_6H_5OH.—This is an aromatic alcohol. A 5 per cent. solution precipitates proteid, and a much weaker solution produces irritation of the tissues, and especially those of the kidney, where its excretion takes place. It is strange that a strong antiseptic like phenol should be a normal product of proteid putrefaction. Phenol is obtainable from tyrosin, by processes of cleavage and oxidation (see Tyrosin), and in the intestinal canal is probably derived from tyrosin. A small amount of the phenol ordinarily absorbed is converted by the organism into pyrocatechin, a dioxybenzol. These two substances are found in normal urine in ethereal combination with sulphuric acid, $C_6H_5O.SO_2.OH$ (or as an alkaline ethereal sulphate). This synthesis, accomplished by the union of the

phenol and sulphuric acid with loss of water, has been obtained by electrolysis, using alternating electric currents.[1] If phenol be administered in more than a very small amount, hydroquinone likewise appears in the urine, paired like the others with sulphuric acid, and should the phenol administered exceed at any time the available sulphate, it forms to a certain extent a synthesis with glycuronic acid, and so combined appears in the urine.

Phenol gives with Millon's reagent (mercuric nitrate in nitric acid with some nitrous acid) a brilliant red coloration. This is given by all bodies having an hydroxyl group on the benzol ring, of which substance tyrosin may be mentioned as an example. It is likewise given by proteid, slowly in the cold, more rapidly on warming, and this fact together with the cleavage putrefactive products has given foundation to the belief that the oxy-benzol ring exists preformed in the proteid molecule.

Pyrocatechin, $C_6H_4(OH)_2$.—This is ortho-dioxybenzol. For its formation see under Phenol.

Hydroquinone, $C_6H_4(OH)_2$.—Para-dioxybenzol. Found in the urine especially in cases of carbolic-acid poisoning (see Phenol). If such urine be shaken in the air, it is turned black, owing to the oxidation of hydroquinone to quinone, $C_6H_4 \begin{cases} O \\ | \\ O \end{cases}$.

p-**Cresol,** $C_6H_4.OH.CH_3$.—This is a product of intestinal putrefaction, and is derived from tyrosin (which see). It is found in the urine as an ethereal sulphate.

Benzoic Acid, C_6H_5COOH.—Salts of this acid and analogous bodies are found especially in plants. In the urine of herbivora therefore is found a considerable amount of *hippuric acid*, $COOH.CH_2.NH.CO.C_6H_5$, the combination of benzoic acid and glycocoll (see Glycocoll, p. 981). On feeding *phenyl-acetic acid*, $C_6H_5CH_2COOH$, phenaceturic acid, $COOH.CH_2.NH.CO.CH_2.C_6H_5$, appears in the urine, while the higher benzyl acids, such as *phenyl-propionic acid*, suffer the oxidation of the side chain in the body, and ordinary hippuric acid is formed. After eating apple-parings and other vegetable substances, hippuric acid is found in human urine. It is further stated that phenyl-acetic acid and phenyl-propionic acids are normal products of proteid putrefaction, though in very small quantities; hippuric acid and phenaceturic acid must therefore be constantly present in traces in human urine. Hippuric acid is split into its constituents by hydrolysis through the action of the *Micrococcus ureæ*.

p-**Oxyphenyl-acetic Acid,** $C_6H_4.OH.CH_2COOH$.—This is a product of the intestinal putrefaction of proteid and of tyrosin (which see). It occurs in the urine either paired with sulphuric acid or as an alkaline salt of oxyphenyl-acetic acid.[2]

p-**Hydrocumaric Acid,** $C_6H_4.OH.C_2H_4COOH$.—This second oxy- acid is likewise derived from proteid and tyrosin (which see) putrefaction. Its occurrence in the urine is similar to the above oxy- acid.

Tyrosin, Amido-hydrocumaric Acid, *p*-**Oxyphenyl-amido-propionic**

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[1] Drechsel : *Journal für praktische Chemie*, Bd. 29, p. 229 ; abstr. *Jahresbericht über Thierchemie*, 1884, p. 77.   [2] Baumann: *Zeitschrift für physiologische Chemie*, 1886, Bd. 10, p. 125.

Acid, $C_6H_4.OH.C_2H_3NH_2COOH$.—Tyrosin is a constant product of the putre-faction of all proteid bodies (except gelatin), and is therefore found in cheese. It may be formed in large quantities by boiling horn-shavings with sul-phuric acid. Leucin is always formed whenever tyrosin is. Tyrosin forms characteristic sheaf-shaped bundles of crystals. All the aromatic bodies thus far described have been eliminated in the urine with their benzol nucleus intact. Tyrosin, however, may be completely burned in the body. This seems to be because of the presence of the amido- group on the side chain, for phenyl-amido-propionic acid is likewise destroyed. Tyrosin is found in the urine in yellow atrophy of the liver, in phosphorus-poisoning, etc. (see Leucin, p. 983). Through cleavage, oxidation, or reduction, the following reactions take place, phenol being the final product.[1] The substances not found in intes-tinal putrefaction are named in italics:

$$C_6H_4.OH.C_2H_3NH_2COOH + H_2 = C_6H_4.OH.C_2H_4COOH + NH_3$$
<div align="center">p-Hydrocumaric acid.</div>

$$C_6H_4.OH.C_2H_4COOH = C_6H_4.OH.C_2H_5 + CO_2$$
<div align="center">p-Ethylphenol.</div>

$$C_6H_4.OH.C_2H_5 + 3O = C_6H_4.OH.CH_2COOH + H_2O$$
<div align="center">p-Oxyphenyl-acetic acid.</div>

$$C_6H_4.OH.CH_2COOH = C_6H_4.OH.CH_3 + CO_2$$
<div align="center">p-Cresol.</div>

$$C_6H_4.OH.CH_3 + 3O = C_6H_4OH\ COOH + H_2O$$
<div align="center">p-Oxybenzoic acid.</div>

$$C_6H_4.OH.COOH = C_6H_5OH + CO_2$$
<div align="center">Phenol.</div>
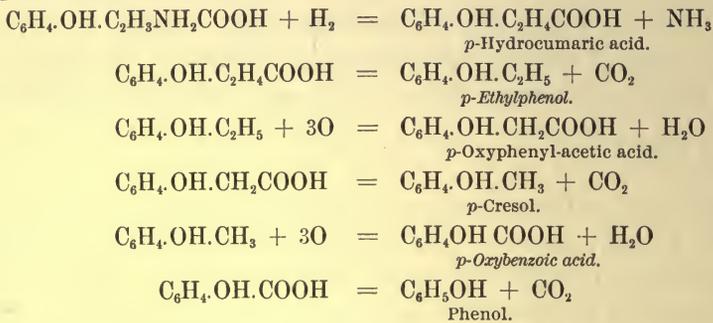
It has never been shown that tyrosin is a normal product of proteid metabolism within the tissues. With leucin it is said to be a normal product of pancreatic di-gestion (see p. 983), being derived only from hemipeptone (Kühne, Chittenden).

Pyridin.—This body has the accompanying formula, one of the CH groups in benzol
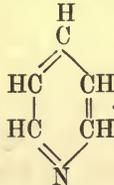
being substituted by N: When pyridin is fed, methyl-pyridin ammonium

hydroxide, $OH.CH_3.NC_5H_5$, is excreted in the urine.[2] This is another case, besides those of selenium and tellurium, of methylation in the body.

Chinolin.—The accompanying formula illustrates the composition
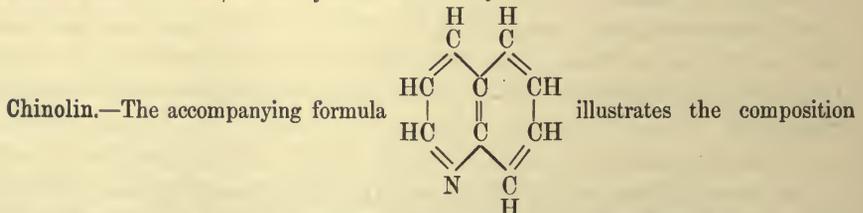
of this body. Several of the methyl-chinolins burn readily in the body.[3]

[1] Baumann: *Berichte der deutschen chemischen Gesellschaft*, 1879, Bd. 12, p. 1450.

[2] His: *Archiv für exper. Pathologie und Pharmakologie*, 1887, Bd. 22, p. 253.

[3] Cohn: *Zeitschrift für physiologische Chemie*, 1894, Bd. 20, p. 210.

Cynurenic Acid, $C_9H_5N.OH.COOH$.—This is oxychinolin carbonic acid; it is found normally in dog's urine, being derived from proteid metabolism. This form of the chinolin group is therefore not burned in the body.

Indol, or Benzopyrol, C_8H_7N.—The source of indol is surely from proteid putrefaction; it may also be obtained by melting proteid with potash.
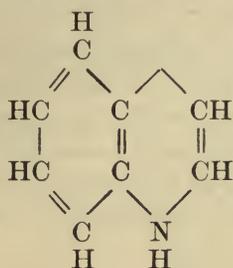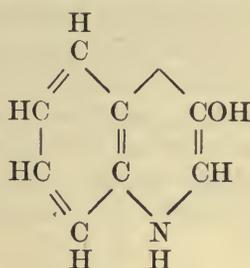
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        H                           H
        C                           C
      //  \    /\                  //  \    /\
   HC      C      CH            HC      C      COH
   |       ||     ||            |       ||     ||
   HC      C      CH            HC      C      CH
      \\  /  \  /                  \\  /  \  /
        C      N                     C      N
        H      H                     H      H
       Indol.                       Indoxyl.
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After its absorption it receives an oxy- group just as benzol does, and like benzol pairs with sulphuric acid with the loss of a molecule of water, and appears as ethereal sulphate in the urine. In preparing indol from feces the fecal odor clings to it. Pure indol, however, has no smell. An alcoholic solution of indol mixed with hydrochloric acid colors fir-wood cherry-red. If urine be mixed with an equal volume of hydrochloric acid, chloroform added, and then gradually an oxidizing agent (chloride of lime), any indoxyl-sulphuric acid present will be oxidized to indigo-blue, which gives a blue color to the chloroform in which it dissolves.

Skatol, or β-Methyl Indol, $C_8H_5CH_3NH$.—The history of skatol,
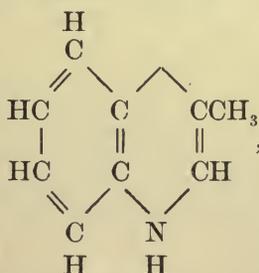
```
        H
        C
      //  \    /\
   HC      C      CCH₃
   |       ||     ||      ,
   HC      C      CH
      \\  /  \  /
        C      N
        H      H
       Skatol.
```

is the same as that of indol. Its source is from proteid putrefaction; after absorption it unites with an oxy- group, and the skatoxyl thus produced pairs with sulphuric acid, and appears in the urine as ethereal skatoxyl-sulphuric acid.

AROMATIC BODIES IN THE URINE.—There have been named above as appearing in normal human urine the ethereal sulphates of phenol, p-cresol, pyrocatechin, indoxyl, skatoxyl, hydroparacumaric acid, and oxyphenyl-acetic acid, of which, however, the last two appear likewise as their salts without being combined with sulphuric acid.[1] These are derived from proteid putrefactive products formed almost entirely in the large intestine (see p. 988), which are partially absorbed and partially pass into the feces. The amount

[1] Baumann: *Zeitschrift für physiologische Chemie*, 1886, Bd. 10, p. 125.

of ethereal sulphate in the urine gives an indication of the amount of intestinal putrefaction. It does not disappear in starvation, mucin and nucleoproteid of bile and intestinal juice furnishing material.[1] If the intestinal tract be treated so as to make it antiseptic, the ethereal sulphates disappear from the urine.[2] Diarrhœa likewise decreases their amount, obviously from the short time given for putrefaction.

Inosit.—This is the hexatomic phenol of hexahydrobenzol, $C_6H_6(OH)_6$. It was long mistaken for a carbohydrate. It has been found in muscle, liver, spleen, suprarenals, lungs, brain, and testicles; likewise in plants, in unripe peas and beans. After drinking much water it may be washed out in the urine, and perhaps for this reason is often found in the voluminous urine of the diabetic. When fed it is burned; also by the diabetic. Its origin is unknown.

SUBSTANCES OF UNKNOWN COMPOSITION.

COLORING MATTERS IN THE BODY.

Hæmoglobin, $C_{712}H_{1130}N_{214}FeS_2O_{245}$ (Zinoffsky's formula for hæmoglobin in horse's blood).—Hæmoglobin is found in the red blood-corpuscle. United with oxygen it forms oxyhæmoglobin, which gives the scarlet color to arterial blood; hæmoglobin itself is darker, more bluish, and therefore venous blood is of a less brilliant red. Methods for preparing oxyhæmoglobin crystals are numerous, but all depend on getting the hæmoglobin into solution. If the corpuscles in cruor be washed with physiological salt-solution, then treated with distilled water, the HbO will be dissolved; on shaking with a little ether the stroma will likewise dissolve; after decantation and evaporation of the ether, at the room's temperature, the solution is cooled to $-10°$ and a one-fourth volume of alcohol at the same temperature added; after a few days rhombic crystals of oxyhæmoglobin may be collected, redissolved in water, and reprecipitated for purification. The crystals may be dried *in vacuo* over sulphuric acid. Once dry they may be heated to 100° without decomposition, but in aqueous solution they are decomposed at 70° into a globulin and hæmatin, the latter having a brown color. This difference in color gives the distinction between "rare" and "well-done" roast-beef. Gastric and pancreatic digestion likewise convert oxyhæmoglobin into a globulin, which may be absorbed, and hæmatin, which passes into the feces. Hæmoglobin is without doubt formed in the body from simple proteids by a synthetic process. (For further information see pp. 973 and 1015, and likewise under the section on Blood.)

CO-**Hæmoglobin** (see p. 960).

NO-**Hæmoglobin** (see p. 956).

Methæmoglobin.—This has the same composition as oxyhæmoglobin. It is found in blood-stains, and may be considered as oxyhæmoglobin which has undergone a chemical change whereby its oxygen is more firmly bound in the molecule.

Hæmatin, $C_{32}H_{32}N_4O_4Fe.$—This is a cleavage-product of hæmoglobin in the presence of oxygen. (See above, under Hæmoglobin). It is not itself a constituent of the body. It is insoluble in dilute acids, alcohol, ether, or chloroform, but is soluble in alkalies or in acidified alcohol or ether, showing characteristic absorption-bands. If a little dry blood be placed on a microscope slide with NaCl and moistened with glacial acetic acid, and warmed, characteristic brown microscopic crystals of *hæmin*, $C_{32}H_{30}N_4FeO_3.HCl$, crystallize out. If these crystals and the spectroscopic test be obtained, one can be absolutely positive of the presence of blood.

Hæmochromogen, $C_{34}H_{36}N_4FeO_5.$—If reduced hæmoglobin be heated in sealed tubes with dilute acids or alkali in absence of oxygen, a purple-red compound is produced called

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[1] Von Noorden: *Pathologie des Stoffwechsels,* 1893, p. 163.   [2] Baumann, *Op. cit.,* p. 129.

hæmochromogen, which is a crystallizable cleavage-product of hæmoglobin. According to Hoppe-Seyler the oxygen in oxyhæmoglobin is bound to the hæmochromogen group. Hæmochromogen treated with a strong dehydrating agent is converted, with elimination of iron, into *hæmatoporphyrin*, $C_{32}H_{36}N_4O_6$, an isomer of bilirubin. Hæmatoporphyrin is said to occur in normal urine.[1] Hæmatoporphyrin treated with nascent hydrogen is converted into a body believed to be identical with hydro- or urobilirubin. Analogous to this is the work of the liver in the body, manufacturing the biliary coloring matter from hæmoglobin, and retaining the separated iron for the synthesis of fresh hæmoglobin (see p. 973). *Hæmatoidin*, found in old blood-stains, is believed to be identical with bilirubin.

The Bile-pigments.—The ordinary coloring matter of yellow human bile is *bilirubin*, $C_{32}H_{36}N_4O_6$. The next higher oxidation-product is the green *biliverdin*, $C_{32}H_{36}N_4O_8$, which is the usual dominant color in the bile of herbivora. In gall-stones have been found the following coloring matters, to which have been ascribed the accompanying formulæ :

Bilirubin (red),	$C_{32}H_{36}N_4O_6$;
Biliverdin (green),	$C_{32}H_{36}N_4O_8$;
Bilifuscin (brown),	$C_{32}H_{40}N_4O_8$;
Biliprasin (green),	$C_{32}H_{44}N_4O_{12}$;
Bilihumin (brown),	?
Bilicyanin (blue),	?
Choletelin (black),	$C_{32}H_{38}N_4O_{12}$.

If nitric acid containing a little nitrous acid be added to a solution of bilirubin, a play of colors is observed at the juncture of the two fluids, undoubtedly depending upon various stages of oxidation. Above is a ring of green (biliverdin), then blue and violet (bilicyanin), red, yellowish-brown (choletelin). Cholotelin is the highest oxidation-product. The above is known as *Gmelin's test*.[2]

If bilirubin or biliverdin is subjected to the action either of nascent hydrogen or of putrefaction it is reduced to hydrobilirubin, $C_{32}H_{44}N_4O_7$. This substance is therefore formed in the intestinal tract, is in part absorbed, and appears in the urine, where it is called urobilin, though the two are identical. Urobilin gives a yellowish coloration to the urine. Injection into the blood-vessels of distilled water, ether, chloroform, the biliary salts, or arsenuretted hydrogen, produces a solution of the red blood-corpuscles and conversion of hæmoglobin into biliary coloring matters which are thrown out in the urine (see p. 988). Bilirubin, biliverdin, and bilicyanin give characteristic spectra.

Melanins.—Under this name are classed the pigments of the skin, of the retina, and of the iris. They contain iron, and their source has been attributed to hæmoglobin. In melanosis and kindred diseases they are deposited in black granules. There are melanins of different composition. In a case of melanotic sarcoma the hæmoglobin was one quarter, the number of blood-corpuscles one-half, the normal, indicating perhaps the source of melanin.[3]

Tryptophan.—This is said to be a cleavage-product of hemipeptone in tryptic digestion ;[4] it gives a red color with chlorine and a violet color with bromine, due to halogen-addition compounds.

Lipochromes.—These include *lutein*, the yellow pigment of the corpus luteum, of blood-plasma, butter, egg-yolk, and of fat; likewise *visual purple* of the retina, which is bleached by light. Solutions of the pure visual purple from rabbits or dogs become clear as water on exposure to light.[5]

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[1] Garrod : *Journal of Physiology*, 1894, vol. 17, p. 348.

[2] For a delicate modification of this test see Jolles : *Zeitschrift für physiologische Chemie*, 1895, Bd. 20, p. 461.

[3] Brandl und Pfeiffer : *Zeitschrift für Biologie*, 1890, Bd. 26, p. 348.

[4] Stadelmann : *Ibid.*, 1890, Bd. 26, p. 491. [5] Kühne : *Ibid.*, 1895, Bd. 32, p. 26.

CHOLESTERIN.

Cholesterin, $C_{26}H_{43}OH$.—This is found in all animal and vegetable cells and in the milk.[1] It is especially present in nervous tissue, in blood-corpuscles, and in the bile. It may be prepared by dissolving gall-stones in alcohol, from which solution the cholesterin crystallizes on cooling in characteristic plates. It is insoluble in water or acids, but soluble in the biliary salts, alcohol, and ether. It is probably excreted unabsorbed in the feces. Cholesterin feels like a fat to the touch, but is in reality a monatomic alcohol. With concentrated sulphuric acid it yields a hydrocarbon, *cholesterilin,* $C_{26}H_{42}$, coloring the sulphuric acid red (Salkowski's reaction). Iso-cholesterin, an isomere, is found combined as an ester with fatty acid in wool-fat or lanolin. The physiological importance of cholesterin is unknown.

THE PROTEIDS.

Consideration of the proteids from a purely chemical standpoint is impossible, for their composition is unknown. There exist only the indices of composition furnished by the products of cleavage and disintegration. Bodies at present classed as individuals may sometimes be shown to be identical, with characterizing impurities. It remains for the chemist to do for the proteid group what Emil Fischer with phenyl-hydrazin has accomplished for the sugars.

As a characteristic proteid, egg-albumin may be mentioned. Proteid forms (after water) the largest part of the organized cell, and is found in all the fluids of the body except in urine, sweat, and bile. Proteid contains carbon, hydrogen, nitrogen, oxygen, sulphur, sometimes phosphorus and iron.

General Reactions.—A neutral solution of proteid (with the exception of the peptones and proteoses) is partially precipitated on boiling, and is quite completely precipitated on careful addition of an acid (acetic) to the boiling solution. Proteids are precipitated in the cold by nitric and the other common mineral acids, by metaphosphoric but not by orthophosphoric acid. Metallic salts, such as lead acetate, copper sulphate, and mercuric chloride, precipitate proteid; as do ferro- and ferricyanide of potassium in acetic-acid solution. Further, saturation of acid solutions of proteid with neutral salts (NaCl, Na_2SO_4, $(NH_4)_2SO_4$) precipitates them, as does likewise alcohol in neutral or acid solutions. Proteid is also precipitated by tannic acid in acetic-acid solutions, by phospho-tungstic and phospho-molybdic acids in the presence of free mineral acids, by picric acid in solutions acidified by organic acids.[2]

Of the *color-reactions* the action of Millon's reagent has been described (see p. 992). Soluble proteids give the biuret test (see p. 1011). With concentrated sulphuric acid and a little cane-sugar a pink color is given when proteid is present (see p. 988). Proteid heated with moderately concentrated nitric acid gives yellow flakes, changing to orange-yellow on addition of alkalies (xantho-proteid reaction). Proteid in a mixture of one part of concentrated sulphuric acid and two parts of glacial acetic acid gives a reddish-violet color (Adamkiewicz), a reaction accelerated by heating. Finally, proteid dissolves

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[1] Schmidt-Mühlheim: *Pflüger's Archiv,* 1883, Bd. 30, p. 384.

[2] The above list is given by Hammarsten, *Physiological Chemistry,* translated by Mandel, p. 18.

after heating with concentrated hydrochloric acid, forming a violet-colored solution (Liebermann).

The following, taken in part from Chittenden,[1] is submitted as a general classification of the proteids:

SIMPLE PROTEIDS.

Albumins
{
Serum-albumin ;
Egg-albumin ;
Lacto-albumin ;
Myo-albumin.

Globulins
{
Serum-globulin ;
Fibrinogen ;
Myosin ;
Myo-globulin ;
Paramyosinogen ;
Cell-globulin.

Albuminates { Acid-albumin ; Alkali-albumin.

Proteoses and Peptones.

Coagulated Proteids { Fibrin ; Other coagulated proteids.

COMBINED PROTEIDS.

Chromo-proteids
{
Hæmoglobin ;
Histo-hæmatins ;
Chlorocruorin ;
Hæmerythrin ;
Hæmocyanin.

Glyco-proteids { Mucins ; Mucoids.

Nucleo-proteids
{
1. Those yielding para-nuclein { Casein ; Pyïn ; Vitellin.
2. Those yielding true nuclein { Nucleo-histon ; Cell-nuclein.

Phospho-glyco-proteids.   Helico-proteid.

ALBUMINOIDS.

Collagen (gelatin).
Elastin.
Keratin and Neurokeratin.

Albumins.—Bodies of this group are soluble in water and precipitated by boiling, or on standing with alcohol. Serum-albumin is the principal proteid constituent of blood-plasma, while lacto-albumin and myo-albumin are similar bodies found respectively in milk and muscle.

[1] "Digestive Proteolysis," *Cartwright Lectures*, 1895, p. 30.

Globulins.—These are insoluble in water, but soluble in dilute salt-solutions. They are coagulated on heating. If blood-serum be dialyzed with distilled water to remove the salts present, serum-globulin formerly held in solution separates in flakes. Fibrinogen and serum-globulin are in blood-plasma and the lymph. Myosin is the principal constituent of dead muscles; in the living muscle myosin is said to be present in the form of myosin-ogen. Myoglobulin in muscle is akin to serum-globulin in plasma. Paramyosinogen in muscle is characterized by the low temperature at which it coagulates ($+47°$). Cell-globulin is also found in the animal cell.

The globulins of vegetable cells are interesting as having been obtained in well-defined crystalline form and in great purity of composition.[1] These are not generally coagulable by heat, and indeed vegetable proteids show many points of divergence from those of the animal.

Albuminates.—If any of the above native animal proteids or any coagulated proteid be treated with an alkaline solution, alkali albuminate is formed. In this way the alkali of the intestine acts upon proteid. If hydrochloric acid acts on proteid, there is a gelatin-ization and slow conversion into acid albuminate, a process accelerated by the presence of pepsin. This takes place in the stomach. Both alkali and acid albuminates are in-soluble in water, but both are soluble in dilute acid or alkali, without loss of individual identity.

Proteoses and Peptones.—These are bodies obtained from the digestion of proteids, through a process of hydrolysis. They are non-coagulable by heat. If a mixture of pro-teoses and peptones be saturated with ammonium sulphate the proteoses are said to be precipitated, while true peptone remains in solution. The chemical identity of this true peptone is still, however, to be established. In gastric digestion are said to exist four varieties of proteoses: (1) Dysproteose, insoluble in water and dilute NaCl solutions, (2) hetero-proteose, insoluble in water and soluble in NaCl solution, (3) proto-proteose, soluble in water and in NaCl solution, (4) deutero-proteose, which is also soluble in water and in NaCl solution, but is distinguished by the fact that while the first-named three are pre-cipitated by saturating the neutral solution with NaCl, deutero-proteose is only partly precipitated, the rest coming down on addition of an acid. Proteoses are converted into amphopeptones, a mixture of hemi- and antipeptone. According to Kühne proteid con-sists of a hemi- and an anti- group, which separate into distinct hemi- and anti- bodies in proteolysis. Of the final products, hemi- and antipeptone, only the former yields leucin and tyrosin in tryptic proteolysis. This is the only radical difference between the two peptones, hence hemipeptone has never been isolated.

Coagulated Proteids.—These are insoluble in water, salt-solutions, alcohol, dilute acids and alkalies, but soluble in strong acids and alkalies, pepsin-hydrochloric acid, and alkaline solutions of trypsin. The chemical or physical change which is effected in coagulation of proteid is unknown.

Combined Proteids.—These consist of proteid united to non-proteid bodies such as hæmochromogen, carbohydrates, and nucleic acid.

Chromo-proteids.—These are compounds of proteid with an iron- or copper-contain-ing pigment, like hæmoglobin, which has already been described. *Histohæmatins* are iron-containing pigments found especially in muscle. That which is found in muscle is called myohæmatin, and resembles hæmochromogen somewhat in its spectroscopic appear-ance, and is believed to be present in two forms corresponding to hæmoglobin and oxyhæmo-globin. It has been regarded as an oxygen-carrier to the tissues. Among the inverte-brates the blood often contains only white corpuscles with sometimes a colored plasma. Thus the blood-serum of the common earth-worm contains dissolved hæmoglobin, that of some other invertebrates a green respiratory pigment, *chlorocruorin*, whose charac-terizing component seems similar to hæmatin; *hæmerythrin* occurs in the pinkish corpus-

[1] Osborne: *Journal of American Chemical Society*, 1894, vol. xvi., Nos. 9, 10; and other arti-cles in the same journal by the same author.

cles of *Sipunculus*, while the blood of crabs, snails, and other animals (mollusks and arthropods) is colored blue by a pigment, *hæmocyanin*, which contains copper instead of iron.

Glyco-proteids.—These consist of proteids combined with a carbohydrate. They are insoluble in water, but soluble in very weak alkalies. On boiling with dilute mineral acids they yield a reducing substance.

Mucins are found in mucous glands, goblet cells, in the cement substance of epithelium and in the connective tissues. Of the nearly related mucoids may be named *colloid*, a substance appearing like a gelatinous glue in certain tumors; *pseudo-mucoid*, the slimy body which gives its character to the liquid in ovarian cysts; and *chondro-mucoid*, found as a constituent of cartilage. On boiling chondro-mucoid with dilute sulphuric acid it yields acid-albuminate, a peptone substance, and chondroitic acid. The last is a nitrogenous ethereal sulphuric acid, yielding a carbohydrate on decomposition, and found preformed in every cartilage[1] and in the amyloid liver.[2] It is, of course, not a proteid.

Nucleo-proteids, or Nucleo-albumins.[3]—These are compounds of proteid with nuclein, which latter yields phosphoric acid on decomposition. If nucleo-proteid, which is found in every cell, be digested with pepsin-hydrochloric acid, there remains a residue of insoluble nuclein, likewise insoluble in water but soluble in alkalies. If this nuclein yields xanthin bases on further decomposition it is called true nuclein, if it fails to yield these bases it is called paranuclein.[4] Nucleo-proteids yielding proteid and paranuclein on decomposition include the casein of milk, pyïn of the pleural cavity, vitellin of the egg, Bunge's[5] iron-containing hæmatogen of the egg, as well as nucleo-proteids found in all protoplasm. They all contain iron. Paranuclein is probably absorbable (see p. 958). It is considered by Liebermann to be a combination of proteid and metaphosphoric acid (see p. 958).

A second group of nucleo-proteids yields true nuclein on decomposition. This group includes the various nucleo-proteids which are constituents of different cell-nuclei. The nuclein here obtained yields on decomposition nucleic acid, from which xanthin bases are always to be derived. These xanthin bases vary in proportion and kind in the different nucleic acids. Nucleic acid of yeast nuclein yields guanin and adenin, that of a bull's testicle adenin, hypoxanthin, and xanthin, that of the thymus adenin alone. Kossel[6] calls this latter "adenylic acid," and speaks likewise of "guanylic," "xanthylic," etc., acids, as provisional names for separate nucleic acids. Each one of this family of acids is capable of combining with any soluble proteid to form nuclein, hence it is readily seen that nucleins may exist in great variety. Another constituent of nucleic acid Kossel finds to be thymin (a body derived from paranucleic acid, which latter, according to Kossel, is a component of paranuclein). Some nucleic acids, such as those derived from yeast, pancreas, and the lactic glands, yield a reducing carbohydrate, while others (calf's thymus) show the presence of the carbohydrate group only in the production of levulic acid after very thorough decomposition, and still others (fish-sperm) fail to indicate any carbohydrate radical as being present. A clearer idea of these relations is afforded by the following schematic view of the decomposition of the nucleohiston, the constituent of blood-plates and of the nuclei of leucocytes.[7]

[1] Mörner : *Zeitschrift für physiologische Chemie*, 1895, Bd. 20, p. 357.

[2] Oddi: *Archiv für exper. Pathologie und Pharmakologie*, 1894, Bd. 33, p. 376.

[3] These two terms are used here as synonymous, though Hammarsten would confine the term nucleo-albumin to those proteids which yield paranuclein. . It is difficult to give a definite classification of these bodies, as the whole subject at present is in a transition stage.

[4] Kossel: Verhandlungen der Berliner physiologischen Gesellschaft, *Archiv für Physiologie*, 1894, p. 194.

[6] *Physiologische Chemie*, 3d ed., 1894 p. 92.   [5] *Loc. cit.*

[7] Lilienfeld : *Zeitschrift für physiologische Chemie*, 1895, Bd. 20, p. 106.

Nucleohiston, soluble in H_2O,
decomposed by HCl or $Ba(OH)_2$ into

Histon, a proteid.

Leuconuclein, an acid ;
decomposed by strong alkali into

Proteid.

Adenylic acid (nucleic acid), which on heating with mineral acids yields adenin, thymin, levulic acid, and phosphoric acid.

(For the respective offices of histon and leuconuclein in the coagulation of the blood, see section on the Blood.)

In the sperm of salmon is found only free nucleic acid uncombined with proteid. According to Kossel other nuclei may at times contain free nucleic acids.

Phospho-glyco-proteids.—This class is represented by Hammarsten's *helico-proteid*, which yields paranuclein, and, unlike other nucleo-proteids of the paranuclein class, it yields a reducing carbohydrate on boiling with acids.

The Albuminoids.—These are bodies derived from true proteid in the body, but not themselves convertible into proteid. They are resistant to the ordinary proteid solvents, and as a rule exist in the solid state when in the body.

Collagen.—This is the chief constituent of the fibres of connective tissue, of the organic matter of bone (osseïn) and is likewise one of the constituents of cartilage. Collagen is insoluble in water, dilute acids and alkalies. On boiling with water it forms *gelatin* through hydration, which is soluble in hot water, but gelatinizes on cooling (as in bouillon). Dry gelatin swells when brought into cold water. By continuous boiling or by gastric or tryptic digestion further hydration takes place with the formation of soluble gelatin peptone. Gelatin fed will not take the place of proteid, but, like sugar, only more effectively, it may prevent proteid waste by being burned in its stead.[1] Gelatin yields leucin and glycocoll on decomposition, but no tyrosin. It therefore gives the biuret reaction, but none with Millon's reagent. It contains but little sulphur. It yields about the same amido- acids as ordinary proteid.

Elastin.—This is very insoluble in almost all reagents and in boiling water. On decomposition it yields leucin, tyrosin, glycocoll, and lysatin. It is slowly hydrated by boiling with dilute acids, and by pepsin hydrochloric acid. It contains very little sulphur, and gives Millon's test. It is found in various connective tissues, and especially in the cervical ligament.

Keratin and Neuro-keratin.—These are insoluble in water, dilute acids and alkalies ; insoluble in pepsin hydrochloric acid, and alkaline solutions of trypsin. Keratin is found in all horny structures, in epidermis, hair, wool, nails, hoofs, horn, feathers, tortoise-shell, whalebone, etc. Neuro-keratin has been discovered in the brain, and in the medullary sheath of nerve-fibres.[2] On decomposition with hydrochloric acid keratin yields all the products given by simple proteids. It contains more sulphur than simple proteid and yields more tyrosin. Drechsel[3] believes that it is transformed from simple proteid by the substitution of sulphur for some of the oxygen and of tyrosin for leucin or other amido-acid. Part of the sulphur is loosely combined, and a lead comb turns hair black, due to the formation of lead sulphide. There are different keratins, and their sulphur content varies greatly.

GENERAL REMARKS ON THE PROTEIDS.—It has been impossible within the limits set to more than glance at the proteid bodies. Many facts concerning the behavior of proteids have been mentioned throughout the text, and

[1] Voit: *Zeitschrift für Biologie*, 1872, Bd. 8, p. 297.
[2] Kühne and Chittenden : *Zeitschrift für Biologie*, 1890, Bd. 26, p. 291.
[3] Ladenburg's *Handwörterbuch der Chemie*, 1885, Bd. 3, p. 571.

cannot be classified here. A list of the principal products of the digestion and putrefaction of proteid may not be out of place. It includes albumoses, peptones, leucin, tyrosin, lysin and lysatinin, aspartic acid, glutamic acid, amido-valerianic acid, volatile fatty acids; phenyl-propionic, phenyl-acetic, *p*-oxy-phenyl-acetic, and *p*-hydrocumaric acids; *p*-cresol, phenol, indol, skatol; and the gases, ammonia, carbonic oxide, sulphuretted hydrogen, methyl mercaptan, hydrogen, and methane.

The size of the proteid molecule must be very great, and one computation shows the following figures:[1]

$$C_{204}H_{322}N_{52}O_{66}S_2.$$
Egg-albumin.

$$C_{726}H_{1171}N_{194}O_{214}S_3.$$
Proteid from hæmoglobin (dog).
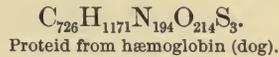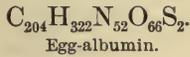
It is well, perhaps, finally, to speak of experiments which, however incomplete, at least throw some light on the possibilities of the problem of the synthesis of proteid. Lilienfeld[2] through the condensation of the ethyl-ester of glycocoll has obtained a body insoluble in water, but swelling in it, forming a gelatinous mass. The substance gives the biuret reaction, is insoluble in alcohol and dilute hydrochloric acid, but dissolves in pepsin-hydrochloric acid. These reactions show its kinship to gelatin. Lilienfeld likewise describes a synthetically formed peptone and a coagulable proteid,[3] the peptone formed principally through condensation of the above-described product with the ethyl-esters of the amido- bodies, leucin and tyrosin, the proteid from the same with addition of formic aldehyde. Grimaux likewise has produced, with other reagents, colloids which resemble proteids. Probably none of these substances are native proteids, but they furnish indications of lines of attack for the future mastery which in time is sure.

[1] Bunge: *Physiologische Chemie*, 3d ed., 1893, p. 56.

[2] Verhandlungen der Berliner physiologischen Gesellschaft, *Archiv für Physiologie*, 1894, p. 383.

[3] *Ibid.*, p. 555.

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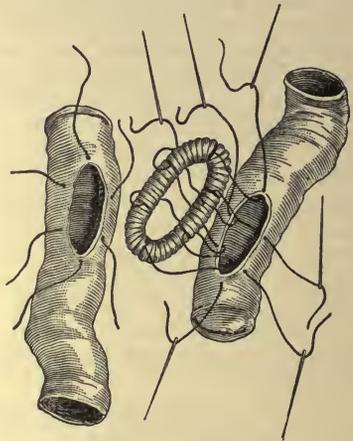
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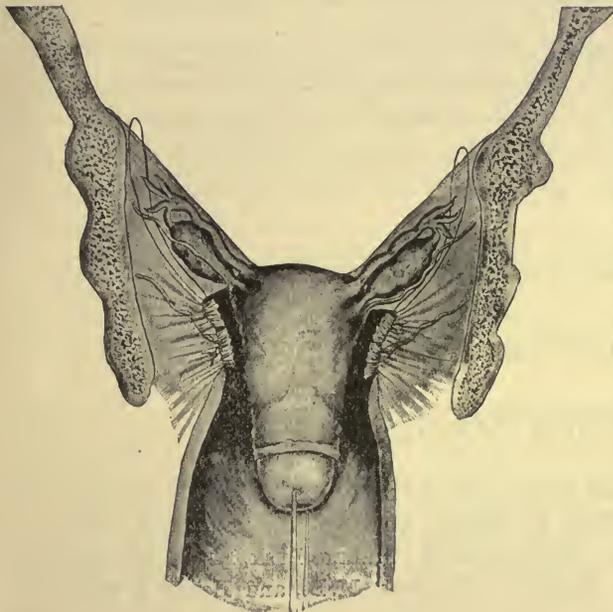
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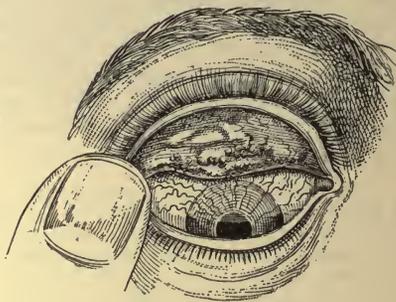
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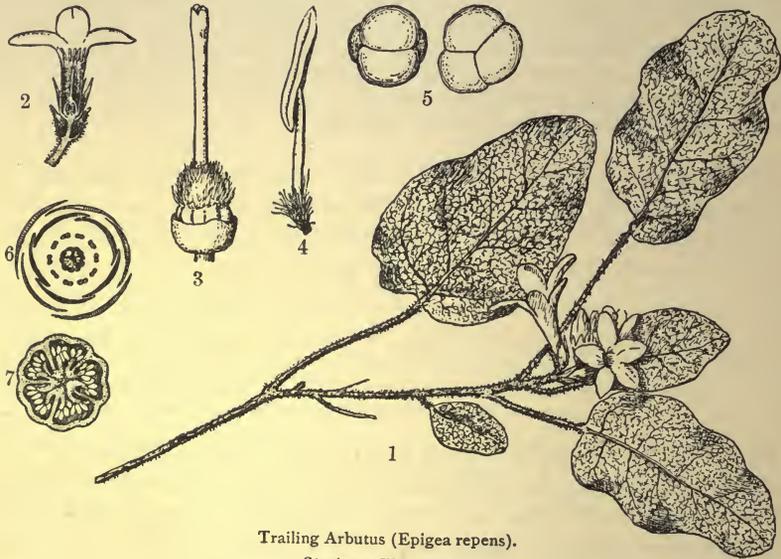
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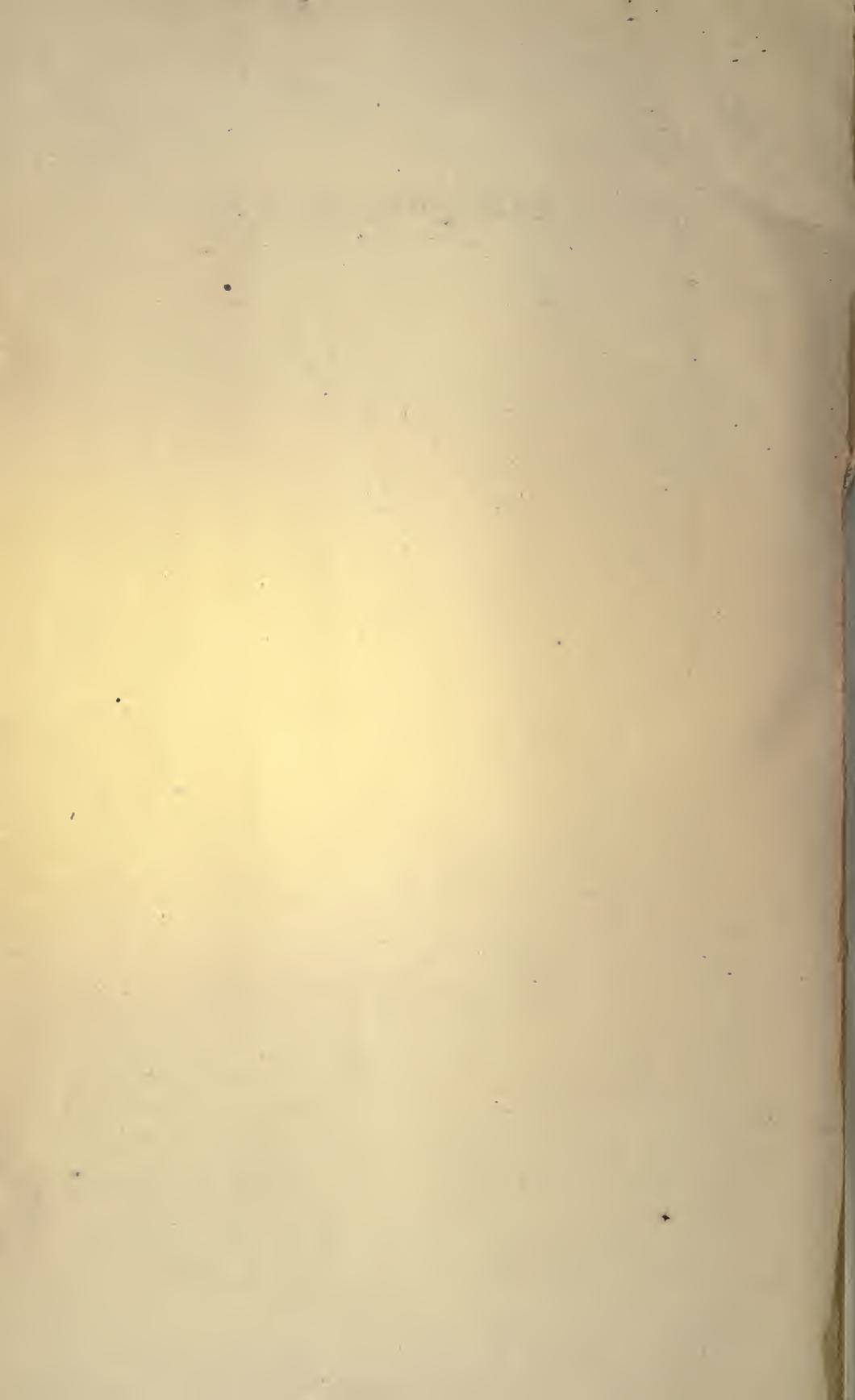
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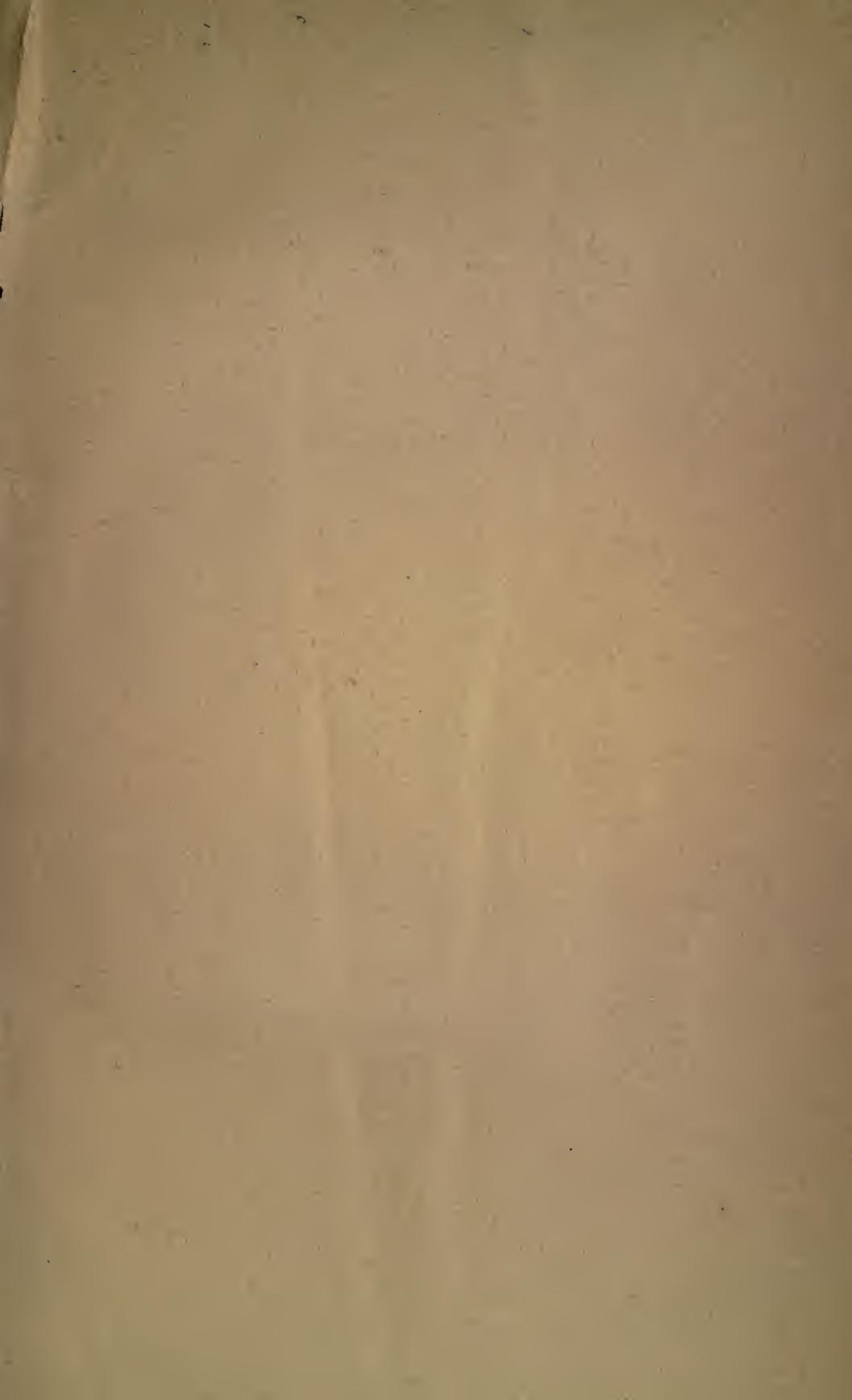3. Size of type and quality of paper and binding.

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