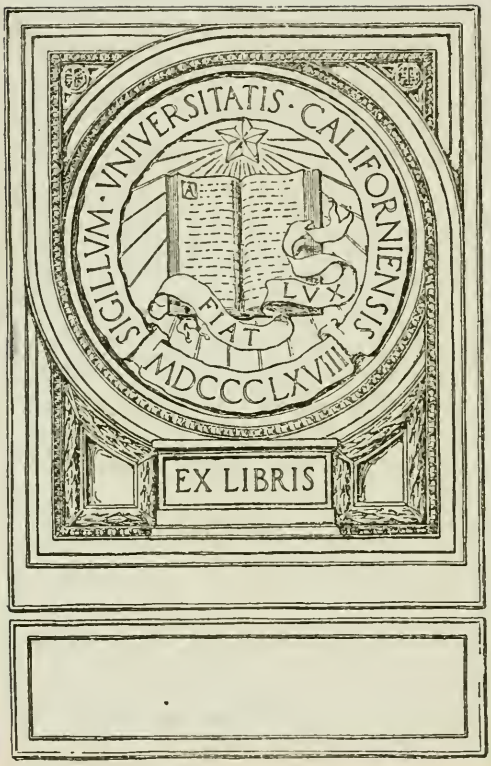

SIGILLVM · VNIVERSITATIS · CALIFORNIENSIS
LVX
FIAT
MDCCCLXVIII
EX LIBRIS

A MANUAL OF PHARMACOLOGY

A MANUAL OF
PHARMACOLOGY

BY

WALTER E. DIXON

M.A., M.D., B.S., B.Sc., D.P.H., F.R.S.

SOMETIME PROFESSOR OF MATERIA MEDICA AND PHARMACOLOGY AT KING'S COLLEGE, LONDON; READER IN PHARMACOLOGY, CAMBRIDGE; EXAMINER IN PHARMACOLOGY IN THE UNIVERSITIES OF OXFORD AND CAMBRIDGE, ETC.

"Dire n'est rien ; faire est tout."—RENAN.

FIFTH EDITION

COMPLETELY REVISED

LONDON

EDWARD ARNOLD & CO.

1921

PREFACE TO THE FIFTH EDITION

The present edition of this manual has been to a great extent rewritten. This change was rendered necessary by the increase of knowledge of the mode of action of drugs which has been obtained during the last few years.

Several new tracings and figures have been introduced into the present volume either to explain new facts or the modern interpretation of facts long ascertained.

My best thanks are due to Professor Ransom and Dr. Inchley for valuable suggestions and criticisms.

W. E. DIXON

July, 1921

PREFACE TO THE FIRST EDITION

It is my object in this Manual to give the student a simple account of the science of Pharmacology, especially in so far as it will enable him to understand the practical application of medicinal agents in the treatment of disease.

Unless the practitioner of medicine has a knowledge of the changes induced in the organism by the drugs that he employs, he must of necessity become a slave to habit and empiricism. He will prescribe in a routine fashion, and drugs will be associated with diseases: his prescriptions will thus become automatic, unreasoned, and without initiative.

Pharmacology, like any other science, cannot stand alone: it is directly dependent upon physiology, chemistry, and pathology, and without a knowledge of these sciences a proper grasp of the subject is impossible. It is not desirable, therefore, that it should enter into the student's curriculum until such time as he has become familiar with the principles of physiology and chemistry. In a sense it may be regarded with general pathology as the connecting link between the purely scientific portion of his training and clinical work, and can be taken most advantageously after he has completed these scientific studies and is commencing work in the wards.

Pharmacology is an experimental science: all we know concerning the mode of action of drugs has been obtained by observations on man and lower animals, and as the experimental method has developed and observations have become more accurate, we find that many of the older drugs have dropped out of practical medicine and have been replaced by others.

For obvious reasons we cannot, except in a very limited number of cases, adopt the experimental method on man, and so our observations have had to be made on lower organisms. And it is not too much to say that nearly all exact knowledge of the mode of action

of drugs has been derived from such experimentation. How great a benefit these discoveries have been to the human race it is impossible to over-estimate: every patient who receives the physician's prescription is deriving advantages from such researches. Pharmacological research has for its object the diminution of human suffering and the prolongation of life: much it has accomplished already, but much more still awaits to be accomplished, and great is the responsibility of those who, either through political motives, ignorance, or hysteria, seek to impede the work.

This is not a text-book on Materia Medica. In former days, when the practitioner had to gather his own simples and make his own preparations from the crude drugs, a knowledge of the characters and physical properties of these crude drugs was absolutely essential. But the duty of collecting, making preparations, and standardising remedies has long since been handed over to the druggist, and now it is of little more importance for the student to be able to recognise a Calabar bean, because he happens to use physostigmine, than for him to be acquainted with the art of printing because he reads. Nor do I consider it desirable that the student should be burdened by committing to memory the composition of various pharmacopœial preparations, especially before such time as he has had opportunities of seeing them prescribed. It is but an encouragement for him to learn, by the aid of *memoria technica*, facts forgotten as soon as the examination for which they are crammed is passed; they serve no educational purpose, and their formulæ are readily accessible.

The therapeutics included in this Manual are only such as serve to illustrate the pharmacology; it is in no sense a book on therapeutics, an art which can be dealt with properly only at the bedside.

It has been my aim throughout to cultivate the reasoning faculties of the student, to accept for granted as little as possible, and to subject all statements to experiment; by this treatment it is hoped that pharmacology may be learnt like any other science, and consist in something more than the mere committal to memory of many disjointed and often unassociated facts, as it has too often in the past.

To aid this object it is especially desirable that the lectures be supplemented either by a series of suitable demonstrations or by practical work. The majority of the tracings shown in these pages were recorded in my class-demonstrations.

The classification which I have adopted still leaves much to be desired. As far as possible, the drugs are arranged in pharmacological groups, but in some instances two drugs which differ entirely in their action have been included in one chapter: thus, in the chapter dealing with the action of drugs on blood-vessels barium and the nitrites are described: these, though in no way related, yet by contrast afford a valuable means of facilitating teaching.

Where possible the doubtful statements have been verified by experiments performed in this laboratory; several of the facts are new, and some of the methods of dealing with the subject are original. When there is any doubt as to the mode of action of a drug, I have generally given the views of the conflicting authorities and their reasons.

In conclusion, I desire to express my indebtedness for the assistance I have derived from the standard works dealing with pharmacology and Materia Medica, especially from those of Schmiedeberg, Husemann, Cushny, Whitla, Wood, Humphrey and White, Stockvis, Brunton, and the text-book edited by Hale White.

My best thanks are due to Professor Langley for permission to reproduce certain figures from the *Journal of Physiology*; to Professor Bradbury for suggestions and criticisms, and for reading parts of the manuscript; and to Dr. Walter Malden for his valuable aid in the revision of the proofs.

W. E. D.

PHARMACOLOGICAL LABORATORY,
CAMBRIDGE
December 1905

CONTENTS

CHAPTER XXX

CHAPTER XXXI

CHAPTER XXXII

DIAGRAMS PRINTED AS PLATES.

Ant

A MANUAL OF PHARMACOLOGY

CHAPTER I

INTRODUCTION

Pharmacology, in its broadest sense, is the science which deals with the alteration of function in living material brought about by changes in its environment: these changes are usually produced by drugs. But the word is also employed in a more restricted sense, as in this book, to denote the science which deals with the action of drugs upon man and without special indications to their application in disease—the latter art, the application of remedies to disease, is termed *therapeutics*. The art of applying drugs to the sick can only be properly studied at the bedside after the student has learned some pharmacology.

The science of pharmacology is based upon the three sciences, physiology, chemistry, and pathology: it is impossible to decide how a drug produces an action until we are acquainted with any, or all, of the factors in these sciences which may be concerned.

Materia medica implies a knowledge of the origin, source, distribution, composition, and preparation of the remedies employed in medicine. It is very important to the druggist, but not in these days to the practitioner of medicine, since the latter no longer has to seek out his own herbs from the woods and fields. The preparations of the crude drugs which he employs are manufactured by the skilled druggist after fixed formulæ published in an official book, the "Pharmacopœia." A practitioner, having chosen the remedies and the doses of them he proposes to give to a certain patient, commits them to paper as a prescription, which is compounded and dispensed by the pharmacist, and the art of preparing such medicines is termed *pharmacy*. It is true there are certain disadvantages in having prescriptions dispensed by unknown pharmacists, and perhaps the most important of these is the risk of stale or otherwise inactive drugs being employed.

A *drug* is a body which modifies the functions of living matter without yielding up energy to it; whilst a food provides the body with useful energy. It sometimes happens that a substance may partake both of the characters of a food and a drug, having a toxic action on some tissue of the body, and also giving up

energy through its oxidation, sufficient in amount for it to be practically useful. Alcohol is such a substance. Drugs and poisons, therefore, may be closely related to foods, and there is no sharp line of distinction between the two groups.

From time immemorial man has been concerned with the cure of disease, and from time to time many systems of cure have been suggested. One of the most ancient, the "doctrine of signatures," required that the external configuration of plants suggested their use in medicine, and hence the origin of such names as lungwort, liverwort, and the like. The celebrated hypothesis of Galen is little more than a mass of fantastic fiction, and deserves no notice. In more recent times, when observations were more accurate, it was noted that symptoms were cured by drugs which produced an opposite effect. Thus, diarrhœa was cured by astringents and constipation by purgatives, and so a system of cure *contraria contrariibus curantur* was promulgated. Towards the end of the eighteenth century a German physician, Hahnemann, introduced *homeopathy*. He regarded disease as "immaterial" produced by some irritation, and being immaterial its symptoms only could be treated: this was done by opposing it with an agent giving rise to a similar series of symptoms, and hence arose another "system of cure," *similia similibus curantur*, and in its support it was pointed out that diarrhœa was sometimes cured by purges, and inflammatory skin diseases by drugs which produced inflammation. This "homeopathic speculation" further suggests that infinitesimal doses—one-billionth of a grain, or less—are necessary to exert this mystic power over disease. Pharmacology is now a purely experimental science, all such fantastic speculations as those mentioned have been swept aside, and it no longer merits the reproach of being a discredit to medicine. It is true that a few medicines are still often prescribed empirically, following the dictates of experience without reference to science: this is the case when colchicum is prescribed for gout. How this drug beneficially affects acute gout the pharmacologist cannot as yet say, but this is largely due to the fact that the pathology of the disease is still unknown. *Rational treatment* presupposes a knowledge of the working of the disease, and the pharmacology of the remedy used to combat it. Quinine, we know, kills organisms of malaria at a certain period in their life-history without hurting the host. The treatment of malaria by quinine is therefore rational, and our knowledge also tells us when to administer the quinine so as to reach the parasite at the one stage in its life-history at which it is vulnerable. Or, to take another example, alkalies administered on an empty stomach inhibit the secretion of gastric juice. If, then, it is discovered that a man is suffering from dyspepsia due to a hypersecretion of a feebly active gastric juice (a common type of dyspepsia), the administration of alkalies is rationally indicated.

It was formerly thought that for each disease a certain cure in

some drug might be found: there are, however, few drugs having such a specific effect over disease, but some exist which may be entitled to the term specific. They are—the various antitoxins, quinine in malaria, mercury and arsenic in syphilis, thyroid gland in myxœdema, sulphates in non-amœbic tropical dysentery, and a few others; but, speaking generally, there is no royal road to curing disease. Having decided as to the exact pathological condition of the patient, we determine how best to assist nature and to prevent death; we may then decide what special tissue of the body must be stimulated or depressed, and from our knowledge of pharmacology select our drug or drugs accordingly. Every case must be decided on its own merits, and the routine use of set prescriptions for diseases is a practice now relegated to the past.

In describing the action of a drug it is well to proceed in a methodical manner. First state what is known concerning the effects of the drug outside the body. Does it influence protozoa bacteria or ferment action? Does it form chemical combinations with proteins? Too much stress can hardly be laid on these simple observations, since they may elucidate the whole action of the drug. To take a single example, the action of tannin depends on its power of combining with and precipitating proteins and gelatine.

The local action of the drug on the skin and mucous membranes should form the next subject of observation. Has it irritant or anæsthetic properties, and does it affect the pupil when applied locally? Having determined these points, the effects of the drug after internal administration should be described. In the mouth, taste salivation and other reflex effects should be noted: a mouthful of brandy has a decided reflex effect on the heart and respiration. In the stomach and intestines the action of the drug should be considered in so far as it affects digestion, muscular movements, vascularity, or gives rise to reflex effects such as vomiting, all these actions being produced before the absorption of the drug into the system. The question of absorption is next considered with special reference to its position and rate; how much, and in what form, does the drug gain access to the blood.

On reaching the blood the drug exerts its *specific action*. That is to say, being now of easy access to all tissues in the body, it generally shows a particular predilection for some special tissue or organ. Strychnine especially picks out certain cells in the spinal cord; pilocarpine excites certain nerve-endings; caffeine has a peculiar affinity for muscle-tissue; whilst quinine has a depressant action on all tissues without a decided specific action on any one. Lastly, the excretion of the drug must be described, the time of excretion and any effect on the excretory organs must be noted, together with any changes which the drug has undergone in the body. Some drugs owe part of their action to changes in their composition; thus citrates and tartrates are excreted as carbonates in the urine, which therefore they render more alkaline.

This is the natural sequence which should be followed in describing the action of a drug; but as many drugs are employed for only one purpose, it must be altered accordingly. Zinc sulphate is an emetic, and is given internally for this purpose only. Its specific action cannot be so determined, because, like many of the other metals, it is hardly absorbed from the alimentary canal. To determine its specific action, it is necessary to inject the drug. Most of the *terms used in Pharmacology* are those found in physiology or are such as readily explain themselves. They are described in detail in their proper position, but one or two may be noticed here. The term "alterative" was formerly used to signify a drug which altered a morbid process: the term is no longer necessary, and should not be used. The term "astringent" is used in a double sense, and refers to remedies which precipitate albumin and gelatine, such as tannin, as well as to remedies which induce vaso-constriction from a specific action on the vessels, such as digitalis. It is wrong to include two such absolutely different groups of drugs under a single title, and it is much better to confine the use of the word "astringent" to the tannin group. The word "tonic" is also a term that is much abused. Strictly, it means a drug which increases tone; and it is well to confine its use to this meaning only. "Stimulant" is another word which is very loosely used. Digitalis, alcohol, strychnine, are all spoken of as cardiac stimulants: such language, except for colloquial use, is of little value. We cannot tell from this if the heart is quicker or slower, or what is the exact condition of systole and diastole. And the same warning applies to the lax use of the word "depressant."

Drugs can affect the function of a tissue only in one of two ways: they may augment or diminish. Oxygen augments the activity of protoplasmic movements, whilst the absence of oxygen soon diminishes it. In some organs containing a complexity of structures it may be difficult to discover whether any given effect is due to stimulation or depression. A drug may quicken the heart by paralysing the inhibitory fibres (vagus) or exciting the accelerator (sympathetic); or again peristalsis can be augmented by cutting off the inhibitory influences (sympathetic) or by stimulating the exciting nerves (vagus); but in each case the result is the same. Alcohol during one stage of narcosis produces hyperactivity of the motor areas, and so does atropine; the effect of the former is probably due to depression of the higher and controlling areas of the brain, whilst that of the latter is a stimulant action on the motor cells—yet the result is somewhat similar in both cases. Strychnine produces convulsions by allowing impulses to pass more easily through the sensory part of the cord, and so a normal impulse induces an exaggerated effect. But we know not if this effect is due to stimulation or depression; nevertheless we speak of the effect as stimulant because the reflexes are increased.

How Drugs Act.—Drugs may produce their effects in one of several ways. Some substances act purely physically. Such, for example, is bismuth carbonate: it is quite insoluble, is chemically inert, and is only absorbed into the system in minute amount from the alimentary canal, and yet it is a valuable drug in conditions of gastric irritation. It acts largely by sticking to the mucous membrane and forming a protective sheath against particles of food and irritating juices. Charcoal is another substance which appears to have a physical action only.

Many chemically inert substances are absorbed and are excreted unchanged. All these substances, provided they form no combinations, specific or general, in the body, exert a greater or lesser narcotic action. A physical law to explain the action of all such substances has been formulated: "The most powerful narcotic substances are those which combine a very slight solubility in water with a very high solubility in ether, olive oil, or brain-lipoid." The cerebral cells are more sensitive to alteration in their composition than other cells, and they contain a much larger percentage of "lipoid matter," so that the drug tends to accumulate in them. Hence, we have another physical explanation of the action of certain remedies. This group will be again referred to when we discuss the action of hypnotics.

There is still a third way in which drugs may profoundly influence the body by physical means—that is, by osmosis. Certain ions are readily absorbed by the alimentary canal, and others are not absorbed and pass out with the fæces. K, Na, Li, NH_4, Cl, Br, I ions are rapidly absorbed into the tissues. SO_4, Mg ions are, on the contrary, only absorbed very slightly. Salts which dissociate into the latter ions will attract to themselves fluid by osmosis until a solution is obtained which is isotonic with the surrounding tissues, and this will render the fæces more watery, and by increasing their bulk tend to augment peristalsis reflexly. In the case of salts which are given in large doses it may be important to determine what part in the action each ion plays; but this is of no significance in the case of the alkaloids; in the case of strychnine sulphate the activity of the strychnine so completely overshadows that of the SO_4 ion that the latter may be neglected.

Most drugs exert their action by chemical, and not physical, means. They may, in the first place, affect tissues chemically in so simple a way that we can understand from our knowledge of chemistry something of what is going on. Concentrated sulphuric acid chars and destroys living tissues in much the same way as it destroys paper or other organic matter, by the withdrawal of water. Or, to take another case, the astringent action of tannin and metallic salts depends upon the combination of these with albumin and the formation of an insoluble albuminate. Or, again, the administration of iron salts cures a deficiency of hæmoglobin (anæmia) in the young. It was believed at one time

that these cases might be due to an excess of sulphide in the gut combining with the organic iron of the food, and so preventing its absorption. Inorganic iron would cure the complaint by combining with the sulphide and forming the insoluble FeS, so that the organic iron, being now left intact, could be absorbed. As one last example of this mode of action we may cite citrates; these salts combine with calcium and fix it. Now calcium is essential not only to living protoplasm, but also to certain unorganised ferments, such, for example, as rennet and fibrin ferment; so that if a little fresh blood is drawn off into a dish containing a few crystals of sodium citrate the clotting of the blood is greatly delayed.

But the drugs which are mainly employed in medicine act in a way different from any of these. Very minute quantities of a drug may induce a general effect on all protoplasm throughout the organism, or may exert an action on some special tissue or tissues, leaving the others quite unaffected. The latter class of drugs, as we have already noted, are said to have a *specific action*, and the former, *i.e.* those which affect most forms of living protoplasm alike, are termed *general protoplasmic poisons*. But even drugs of the latter class exert some specificity. Thus cocaine and aconitine paralyse sensory nerve-fibres before motor; and quinine in minute amounts will destroy the spirochætæ of the mouth, whilst having no effect, even in ten times the concentration, on those found in the blood taken from a case of relapsing fever.

It is suggested that during the production of a specific effect the active drug is in some sort of combination with a chemical body contained in the cell acted upon; and it is generally assumed that this combination is chemical in character. For example, we know that adrenaline is taken up and destroyed by the nerve-endings which it excites; and further, that only a limited amount is so taken up, for when this limit is reached the adrenaline remains unchanged in the blood. Or, again, secretin is taken up by the pancreas cells, and the chemical combination which results induces the active secretion of the gland. In the examples we have given the drug is destroyed as a result of the chemical change. This is, however, not always the case. Strychnine, for example, which has a specific effect on the cord, either is not chemically combined or enters into some very loose combination, for all the alkaloid may be subsequently recovered in the urine, though excretion may last several days. If strychnine is mashed up with fresh spinal cord the alkaloid is quite easy to recover again, but if secretin is shaken up with a pancreatic emulsion, or if adrenaline is passed several times through some vessels containing a plentiful supply of nerve-endings, the drug in each of these two cases is destroyed. Morphine, an alkaloid acting essentially on central nerve-cells, takes a place in between strychnine on the one hand and adrenaline and secretin on the other. It is partially destroyed in the tissues; but if the animal is tolerant to morphine the destruction is much greater than normal.

Ehrlich suggested an hypothesis to account for the action of toxins on the tissues. He believed that the specific effect of toxins on special tissues was due to the possession of side-chains on the "biogen-molecule," to which the molecules of the toxins attached themselves in the same way that he considers that nutritive proteids are capable of uniting to cells during normal assimilation. As regards drugs, it is difficult to suppose them acting in this way, and it is an easy matter by using suitable solvents to remove such drugs from the tissues, *i.e.* they are recoverable, which toxins and foodstuffs are not.

It is necessary at this stage to understand what is meant by *protoplasm*. Put crudely, we mean a collection of dead matter constantly undergoing certain chemical changes, both anabolic and katabolic, in a definite order. Now these changes, taken as a whole, are very complex, but when analysed as far as we are at present able to do, they consist of an immense number of simple chemical reactions which probably all fit into one another and follow one another in a regular sequence. If we pick out from this sequence any one single change and examine it more in detail, we find in a certain number of cases that we can imitate in the laboratory this change which the living protoplasm brings about in the body. This we do, not through a known chemical reagent, but by means of a body termed a ferment. Ferments can be obtained in indefinite numbers from all living structure; thus about fifty have already been extracted from the liver. It is very probable, then, that living matter produces its internal changes through the agency of ferments, each, no doubt, having a comparatively limited sphere of action, and passing on its products when acted upon to be dealt with by another ferment, and so on, no matter whether the changes are anabolic or katabolic in nature. If we remove from a living cell all dead material, water, salts, and ferments, is it necessary to assume that there is anything left? We think not, and believe that there is no inherent difficulty in regarding protoplasm as a system of ferments co-ordinated together. Dead material to which ferments are added does not, however, constitute life, even should fermentations occur, because co-ordination between the different ferments is lacking.

If, then, we regard protoplasm from some such simple standpoint, it is obvious in what a great number of ways drugs may act on the living cell: they may have an affinity for any of the dead particles undergoing analytical or synthetical reactions, and thereby either stop or accelerate the cycle of changes, or they may produce their effects on the ferments. Thus the action of invertin upon cane-sugar is hindered by KCl, quickened by NH_4Cl, and unaltered by a certain proportion of both salts. We can understand why glucose is oxidised in the body or converted into glycogen by ferments which have no action on other sugars such as xylose; the latter, therefore, passes through the system unchanged. Caffeine

has a special action on muscle, whereby death and rigor mortis of the fibres are induced. But this is due to a greatly accelerated ferment action resulting in a large liberation of lactic acid, too much for the muscle to deal with in the ordinary way by oxidation ; the acid coagulates the myosinogen and myosin is formed. The caffeine does not itself seem to partake directly in the chemical action.

This simple conception of protoplasm will explain all the phenomena with which we are directly concerned in pharmacology.

A drug may have a specific action, not necessarily of the same kind, on several tissues. Atropine excites the cells of the motor cortex, but it depresses the vagal endings in the heart. And even in the same cell drugs do not influence all processes to the same extent. Thus, to take an easy example, certain vegetable cells show both movements of the protoplasm and karyokinetic figures in the nucleus. Certain gases and poisons not too concentrated inhibit the moving protoplasm, but do not stop the karyokinesis.

Weights and Measures

The English official standards of weights and measures as prescribed by the "Pharmacopœia" are those of grains, minims, drachms, and ounces. In foreign countries the metric system is in general use and liquids as well as solids are weighed. The metric system is universally known, is very easy, and it has a simple relationship between linear, solid, and liquid measures. The 1915 "Pharmacopœia" makes both systems official. The new "Pharmacopœia" has also introduced the words mil, decimil, centimil, to represent 1 cubic centimetre, one-tenth and one-hundredth of a c.c. respectively.

WEIGHTS (*Avoirdupois Weight*).

1 grain	. . . . .	Symbol, gr.	
437·5 ,,	= one ounce	. . . ,,	℥
16 ounces	= one pound	. . . ,,	℔

The drachm is also generally employed, but it is not official ; it represents 60 grains, and is written ʒ.

MEASURES OF CAPACITY.

1 minim (5.9192 centimils)	. . . . .	Symbol, ♏	
60 minims (3.5515 mils)	= one fluid drachm	. ,,	ʒ
8 fluid drachms (28.412 mils)	= one fluid ounce	. ,,	℥
20 fluid ounces (0.5682 litre)	= one pint	. . ,,	O
8 pints (4.5459 litres)	= one gallon	. . ,,	C

1 minim (5.9192 centimils)	= 0.911 grain of water at 62° F.	
1 fluid ounce (28.412 mils)	= 473.5 ,, ,, ,,	
1 per cent. solution	= about one grain in 110 minims	

In the household, medicines are often roughly measured by assuming that a drop = ℥ i, a teaspoonful = ʒi, a dessert-spoonful = ʒij, a table-spoonful = ½ʒ or ʒss (ss = semisse), a tumblerful = ʒxi.

CONVERSION OF BRITISH TO METRICAL.

Weights.

1 grain	=	0.065 grm.	= 6.5 centigrms.
1 ounce	=	28.349 grms.	

Measures.

1 minim	=	0.059 c.c.	= 5.9 centimils.
1 drachm	=	3.55 ,,	= 3.55 mils.
1 fluid ounce	=	28.417 ,,	= 28.417 mils.
1 gallon	=	4.545 litres.	

CONVERSION OF METRICAL TO BRITISH.

1 gramme	=	15.432 grains.
1 cubic centimetre (1 mil)	=	16.95 minims.
1 litre (1000 c.c.)	=	35.275 fluid ounces, or 1.76 pints.

CONDITIONS MODIFYING THE ACTION OF DRUGS

The " Pharmacopœia " suggests *doses* for each drug which may be used as guides, but the dosage in any particular case is affected by many different factors. A drug may have different actions according to the dose in which it is given. Thus, ammonium carbonate is an expectorant in small doses (3 to 10 grs.), but in doses of 30 grs. it is emetic. Or, to take another example, aconitine in therapeutic doses slows the heart-beat by stimulating the medulla; but if the dose is increased much the heart becomes very rapid, because the direct action of the drug on the cardiac muscle obtains sway.

When a drug produces some definite effect on a tissue, the degree of action varies with the quantity of drug which is free to act, or, in other words, with the relationship between the amount of tissue acted upon and the drug acting. As most tissues grow larger with *age*, it is obvious the amount of drug suitable to produce an effect in an adult may be too great for a child, so that, strictly speaking, the amount of any drug to be prescribed should be in proportion to the weight of the patient. In practical medicine this refinement is not observed. But there are several rough-and-ready rules for estimating, from the adult dose, suitable ones for children. One such method is to add twelve to the age of the child and divide the age by the amount thus obtained, the quotient being the fraction of the full dose which may be given. Thus, for a child of three years old $\frac{3}{3+12} = \frac{1}{5}$. But no rule of this description is infallible, since the structures of the body do not develop in equal

proportion ; some are still embryonic whilst others are practically mature. We find that opium even in extremely small doses is very toxic to children, and the central nervous system upon which the opium acts is one of the last tissues to reach maturity. Indeed, it may be stated as a general rule that such differences in action as occur between adult man and children, or between man and other mammals, are due to a difference in structure, and in consequence it is the drugs which specially affect the higher brain which exhibit the greatest variations of action. Drugs which attack the heart or nerve-endings, structures which are almost identical in all mammalia, act in much the same way throughout the animal kingdom.

The relationship between the *time of administration* of the drug and meal-time may influence not only the rate of absorption of the drug, but may also in some cases modify its action. When drugs are given on a full stomach absorption is likely to be slower than if they are given some hours after a meal. Should a local action be desired on the gastric mucous membrane the drug, such as bismuth, must be administered before food. Drugs containing tannin, on the other hand, should be prescribed after meals : if they are given on an empty stomach the tannin, which normally combines with the albumin of the food, will now irritate the stomach and induce vomiting. Similarly, a full dose of arsenic before a meal will induce gastric irritation, but it has no disagreeable effect if taken immediately after food. As a final example, we may mention the alkalies. If these are taken before food they inhibit the secretion of gastric juice, but if taken some time after a meal they may be used to neutralise excess of acid in the stomach and have no inhibitory effect.

Pregnancy and *lactation* should be taken into consideration when prescribing. Strong purges reflexly increase the movements of the uterus and may lead to abortion. During lactation many drugs are partially excreted by the milk, and so may affect the child, and in some cases even lead to poisoning.

The *preparation* employed is also a matter of importance. Thus, the infusion and tincture of digitalis have a different action. Whenever possible a standardised preparation should be used, *i.e.* either the pure alkaloid or, when this is impossible, a preparation which has been otherwise standardised. Ergot, digitalis, and Indian hemp are especially liable to wide variations in activity.

Drugs sometimes appear to have a different effect in *disease* from their normal action. This is not really the case ; they act in precisely the same way, although the results may appear different. Digitalis produces decided slowing of the heart in those forms of cardiac disease in which the beat is very rapid, but it only slows the beat a little in health. It slows a normal heart-beat of 80 more than one of 60, and since digitalis excites the vagus we can understand why the slowing is so much more pronounced in the

quick heart of mitral disease than in the normal heart. Part of the cardiac slowing is also due to an action of digitalis on cardiac muscle. Pilocarpine produces sweating by exciting the nerve-endings to the sweat-glands. Yet if the spine is fractured and the cord crushed the sweating produced by pilocarpine is very deficient below the seat of fracture. The normal action of the drug in this case is possibly over-shadowed by inhibitory impulses. As other examples, we mention thyroid gland, which cures myxœdema, a disease which is produced by a deficiency of thyroid secretion; morphine in the morphomaniac; antipyretics in fevers, and the various antitoxins, all of which will be considered in detail later. In general toxæmias such as typhoid and diphtheria all drugs lose much of their action. Thus in severe cases $\frac{1}{2}$ gr. strychnine, enough to cause convulsions and even death in a normal person, may be without appreciable effect.

The *time* to administer a drug requires consideration. Hypnotics should be given at a suitable interval before bed-time; purgatives are best taken in the evening, and so on.

Drugs may exert an unexpected effect either by having an unusual action or by failing to produce their ordinary action. Some of the so-called cases of *idiosyncrasy* admit of easy explanation. Many plants contain more than one active constituent, and if one of the rarer of these happens to be present in excess untoward symptoms may result. Opium should contain about 10 per cent. of morphine and act as a narcotic, but sometimes narcotine is present in very large amounts, even up to 15 per cent., and may then lead to excitement or even convulsive spasms. Or the drugs may deteriorate by keeping. Some of the evil effects may depend on cumulation due to deficient excretion, as in renal disease. But there are some idiosyncrasies which no foresight can anticipate. In some people the smell or sight of a cat induces an attack of asthma, and the fact of eating a single strawberry has been known to produce swelling of the face, attacks of faintness, and even death. Slight alterations in the composition of the tissue fluids may cause these conditions; for example, a deficiency in calcium renders the whole autonomic nervous system more susceptible to the action of drugs.

The drugs which more usually manifest these idiosyncrasies are quinine, the iodides, opium, belladonna, and the antipyretics of the coal-tar series. Some patients exhibit toxic symptoms after therapeutic doses of opium, some get buzzing noises in the ears after small amounts of quinine, and others are invariably made wretched by minute doses of mercury.

Some cases of idiosyncrasy may be explained by *cumulation*. Some drugs are excreted more rapidly than they are absorbed, and with these it is difficult to get sufficient drug present in the blood at one time to produce a specific effect. Such is the case with curare and potassium salts. Neither of these when administered

by the mouth in moderate doses shows its specific action, but if they are injected so that their rate of absorption exceeds that of excretion, the former paralyses motor nerve-endings and the latter depresses muscle-tissue, more especially that of the heart.

Cumulation is the opposite effect to this. Small doses of certain drugs constantly repeated may produce quite suddenly symptoms of such a nature as to suggest either the absorption of a large dose of the drug or a temporary deficiency in the excretion. Lead is only absorbed in minute quantities, but if these quantities are absorbed regularly, symptoms of lead poisoning, colic, and paralysis are produced after a certain time. During the period of absorption the drug is not excreted at the same rate that it is absorbed, so that it accumulates in the tissues until a certain saturation point is reached, when it suddenly produces poisonous symptoms. In some cases, no doubt, the sudden symptoms which develop during the exhibition of a drug may be due to an accelerated absorption, the result, say, of some accidental gastric effect ; and in others to a deficient excretion possibly due to irritation of the kidney involving vaso-constriction.

It has been suggested that cumulative action may be a " summation " effect, and not necessarily due to the accumulation of the drug in the tissues ; and it is stated that the susceptibility of an animal to strychnine, a drug which induces convulsions, increases with its continued administration. But strychnine is very slowly excreted, and so the increased susceptibility is more likely due, even in this case, to an accumulation of the drug in the tissues than to a summation of effects. Cumulation is frequently seen with mercury, lead, arsenic, iodides, and digitalis.

TOLERANCE AND IMMUNITY

Some animals and men fail to react to certain drugs in what should represent a considerable dose, and this phenomenon is spoken of as tolerance. Tolerance may be either natural or acquired. The rat is very tolerant to digitalis, birds to opium, the rodents generally to emetics, the herbivora to atropine, and hedgehogs to opium, cyanides, arsenic, mercury, cantharides, and other poisons. Let us take as an example that of the resistance of the hedgehog to cantharides. In the first place, it is easily demonstrated that there is no absolute tolerance, but the tissues of this animal suffer much less from this inflammation-producing drug than those of other animals. Cantharidin, the active constituent, is absorbed into the tissues, and is excreted unchanged by the kidneys, and yet there is no inflammation of these organs such as occurs in almost every other animal. Such a resistance must be specific, for other drugs which are renal poisons, such as potassium chromate, are as poisonous to these organs in the hedgehog as in the rabbit. We are still ignorant as to the cause of such tolerance, but

judging from analogy we might regard the diminished activity as being due to a chemical combination of the cantharidin with some constituent of the cell which renders it non-toxic and in a suitable form for excretion.

Natural tolerance may be due to a greater power of excretion than absorption, as is the case with curare, and potassium ion, neither of which is poisonous when given in moderate doses by the mouth. Or it may be due to a power of neutralising the poison ; thus, if a quantity of dilute acid is administered to carnivorous animals, instead of this being neutralised by the fixed alkalies of the blood and tissues, as is the case in herbivorous animals, it is neutralised by the ammonia which is liberated by the tissues. Much larger amounts of dilute acids may, therefore, be absorbed by man and the carnivora than by the herbivora. This is a very important tolerance, since acid is particularly liable to be present in flesh-eaters, and were they not protected by the formation of ammonia they would gradually be deprived of all their alkaline salts. Chickens are immune to oxalic acid when given by the mouth because their intestines contain so much calcium. Any condition which lowers the general resistance of an animal increases its susceptibility to poisons. If a frog is warmed in tepid water it becomes much more susceptible to drugs and toxins. Or, again, animals may be killed by administering cholera organisms with the food, if peristalsis is previously stopped by morphine or if the gastric juice is neutralised by sodium carbonate, but not otherwise.

Acquired tolerance is the result of habituation to the drug, and it is frequently very difficult to explain. When a solution of one of the heavy metals, such as zinc sulphate or copper sulphate, is taken by the mouth, the albuminate is formed and the acid is set free in the stomach. These two factors, the formation of the precipitate and the liberation of free acid, serve to produce a corrosive effect. But if non-lethal doses of such salts are taken habitually they soon cease to have effect ; the mucous membrane becomes tolerant to the effect of the acid. How this is affected is not known, but the condition is in a general way analogous to the thickening of skin which may be induced in any part of the body as a result of constant irritation.

There is little doubt that some degree of tolerance to arsenic may be developed by habituation. The peasants in parts of the Austrian Tyrol take arsenic to improve their powers of endurance. They are stated to begin with doses varying from one-sixth to one-eighth of a grain, which are gradually increased till four or five grains are taken at a dose. Animals also may be habituated in a small degree to arsenic, but the tolerance is difficult to obtain and the animals often die in the process. The explanation of such tolerance is not easy.

Cloetta found that dogs could receive by the mouth gradually increasing doses of arsenic without poisonous symptoms. If, however, the administration were stopped and a dose much smaller

than that given by the mouth were injected subcutaneously, grave symptoms of poisoning set in and the animal died.

Yet this deficient absorption is not the whole explanation, for some arsenic is absorbed even in the most tolerant man, since it can be recovered from the urine; why then does it not exert its specific effect in these cases? One hypothesis which has been suggested is that an antitoxin is formed by the habitual administration of the drug. This "anti" body is said to be present in the blood serum, for 8 c.c. of the serum from a tolerant rabbit when injected into a normal rabbit will avert death in the latter, after it has received a minimum lethal dose of arsenic. This evidence is not conclusive, since the injection of almost any protein increases the resistance of animals to drugs. Nevertheless it assists us in forming an explanation of the tolerance. The action of arsenic depends upon its ionisation, and if it combines in the body and forms a compound which will not ionise, of which several such are known, its action at once ceases; but the body with which it combines is not an "antitoxin," in the sense in which the word is now used. In support of this suggestion, we know that arsenic is excreted in the urine in some organic form. Perhaps as an analogy the action of carbolic acid in the body is suggestive. This substance when injected into the blood of an animal uses up the sulphates and is excreted rapidly as phenyl-sulphuric acid, a comparatively non-toxic substance; but as soon as the sulphates are used up symptoms of general poisoning supervene: salicylic acid combines in the animal body with glycocoll, and the resulting salicyluric acid is non-toxic and readily excreted; chloral, camphor, and numerous benzene derivatives combine with glycuronic acid, forming in each case less poisonous derivatives. The tolerance of arsenic, which it should be remembered can only be developed to a very limited degree, can be explained (1) by its effect on the alimentary canal, as in the case of the other metals, and non-absorption, and (2) after absorption by its combining to form some non-ionisable organic body which is readily excreted.

The best examples of tolerance in drugs are seen in many of the organic substances, such as morphine, nicotine, or alcohol.

Moderate doses of alcohol are oxidised in the body, and probably only 1 or 2 per cent. is excreted unchanged; this oxidation must be regarded as a protective process. If a man unaccustomed to taking alcohol is in a condition of nitrogenous equilibrium, *i.e.* he is taking in just as much nitrogen as he gives out, the effect of adding a fairly large dose of alcohol to his dietary is to increase nitrogenous loss, which must indicate a poisonous action of the drug; but if the drug is continued, after three or four days this effect disappears and there is a slight gain of nitrogen to the body. The toxic effect has gone and the tissues are capable of oxidising the drug more easily; or, put in another way, tolerance has been developed. Whether this oxidation is brought about by a ferment (oxydase) we have not yet

sufficient evidence to show. Habituation when acquired for a particular drug sometimes produces tolerance to allied drugs; thus, drunkards require more chloroform to produce anæsthesia than temperate people, not on account of an increased destruction of the drug, but because of structural changes in the brain.

The habitual consumption of opium or morphine also leads to tolerance; the interruption of the daily dose, when once established, produces nervous and bodily misery. It has been shown that if dogs are injected hypodermically with morphine, about 70 per cent. of the drug can be recovered from the fæces. If the same dose is repeated many times, the amount that can be so recovered gradually diminishes until eventually none can be obtained. If, now, the dose is increased, the same phenomena happen again with the surplus morphine until once again a stage is reached when none is excreted; in this way one or more lethal doses may in time be given without ill-effect, although the ordinary symptoms of morphinism can still be obtained by further increasing the dose. If such a tolerant animal is killed no morphine is found in its tissues, and hence the tissues must destroy the alkaloid by oxidation. An emulsion of the liver from a tolerant animal incubated with morphine at body temperature destroys more alkaloid than a normal liver emulsion under identical conditions. We know that the weapons of the living cell, by means of which it deals with incoming materials, are bodies we term ferments, and although we cannot yet speak certainly as to whether this transformation is brought about by direct effect of an oxydase, yet it would seem very probable.

Nicotine and atropine are other examples of drugs in which tolerance after habituation is probably to be explained in a similar fashion. Everyone knows that nicotine to the novice at first induces nausea, vomiting, and makes him feel generally ill, but if tolerance is acquired, large amounts may be absorbed without any noticeable ill-effect. The natural tolerance of the rabbit to atropine and the intolerance of the cat depend on both rate of destruction of the alkaloid in the body and rapidity of excretion.

It has been stated that if a drug is applied only to a certain organ of the body this organ alone will after a time become tolerant Thus, atropine, if continually dropped into the conjunctiva, soon ceases to induce its normal effect, and more atropine is requisite to induce dilatation of the pupil. It is questionable if this is a tolerance. Atropine attacks the nerve-endings of the third nerve, and if these fibres are kept paralysed on and off, secondary changes are produced in the circular muscles as well as on the radiating fibres, and paradoxical effects ensue.

A few words may be said here on the antagonism between toxins and antitoxins. It is advisable to retain the word "tolerance" to such simple bodies as alkaloids, and to confine the term "immunity" to a condition brought about by the production of "anti" bodies. By injecting toxins, or protein poisons, into animals, bodies are formed

in their tissues which render the toxins inert; these are termed antitoxins. They are specific and protect against one toxin only. The two substances, toxin and antitoxin, combine together chemically, as was shown by Martin and Cherry, in the following way:— Diphtheria toxin passes through a Berkefeld filter covered with gelatine, but antitoxin does not because its molecule is too large. If the toxin is mixed with the antitoxin and kept at a suitable temperature a short time the toxin no longer passes through the filter, showing that some chemical combination has occurred.

If an animal which is immune to a toxin is bled and the serum collected, this will be found to contain the antitoxin, which when injected into another healthy animal renders it immune to the specific toxin. Ricin and abrin are vegetable protein-poisons of enormous potency and exert a necrotic action at the seat of inoculation. If mice are fed on these bodies, such a degree of immunity is developed in a few weeks that the animals can then tolerate 400 times the original fatal dose given by subcutaneous injection.

If an animal receives a first injection of some foreign protein not sufficient to produce any observable effect, a second injection some three or four weeks later renders the animal extremely ill and often causes death from circulatory failure. This supersensitiveness is known as *anaphylaxis*.

Some people exhibit supersensitiveness to foods; some cannot eat eggs, especially if they are lightly boiled, because cutaneous rashes, migraine, and alimentary disturbances occur. It is worth noting that such an alimentary anaphylaxis to eggs has been obtained experimentally. Mussels, plaice, crayfish, oatmeal, strawberries, and other foods occasionally cause similar effects. In the supersensitive these symptoms are rapidly and certainly produced; minute doses only are required, and the symptoms are identical with those which are seen in the lower animals produced by experimental anaphylaxis. The tuberculin reaction in the tuberculous may be regarded as an example of anaphylaxis.

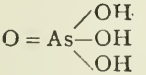
PHYSIOLOGICAL ACTION AND CHEMICAL CONSTITUTION

The specific effect of a drug usually depends upon its chemical interaction with some constituent of the living cell. The latter factor is generally unknown, and can rarely be subjected to chemical analysis. The chemical constitution of the former may be well recognised and its pharmacological action, as well as that of several of its derivatives, accurately determined. Great things were expected formerly from a comparison of a number of closely allied chemical bodies in relationship to their pharmacological action, and the future of pharmacology was regarded as synthetical, *i.e.* the building up to order of chemical substances which would have a pharmacological action previously determined upon, and

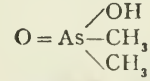
not the mere analysis of an action of a chemical compound having a known constitution. In such suppositions the vital factor is not sufficiently recognised. Minute changes in the living substance, which cannot be detected by any means at our disposal, may yet induce an entirely different action of drugs. Quinine is toxic to the fresh-water amœba in doses of 1 in 50,000, but even 1 in 1000 is not very toxic to the sea-amœba.

The physical properties of a drug also influence its physiological action. When the composition of a drug is altered, be it never so little, its physical characters also change, its volatility, solubility, osmotic properties, ionisation, all or any of which may considerably modify its pharmacological action. Yellow phosphorus given by the mouth is a violent poison, but red phosphorus, which differs from it mainly as regards its physical properties, is comparatively innocuous. And this alteration in physical characteristics is sufficient to explain the whole difference in pharmacological action. The action of certain hypnotics affords another example of the influence of physical characters on pharmacological action. We have already noted that they may be chemically inert bodies, which are absorbed into the system and pass out unchanged, but which on account of their ready solubility in fat-like compounds tend especially to collect in those parts where such bodies exist, *i.e.* the central nervous system ; in this way they interfere with the proper working of the nerve-cells. The chemical constitution of hypnotics of the latter group is but an index of their physical properties, such as their relative solubility in the various tissues of the body, and of osmosis.

The physiological activity of a salt depends on various factors, and first on the amount of dissociation which it undergoes in solution ; those which do not ionise are relatively inert ; they have a mass action only. Such are potassium ferrocyanide and zinc ethyl, $Zn(C_2H_5)_2$. The disinfecting power of mercury salts varies with the amount of dissociation, and not with the quantity of mercury in the solution ; and the toxicity of acids and alkalies varies with the amount of (H) and (OH) ions respectively which are present.



Arsenic acid.



Cacodylic acid.

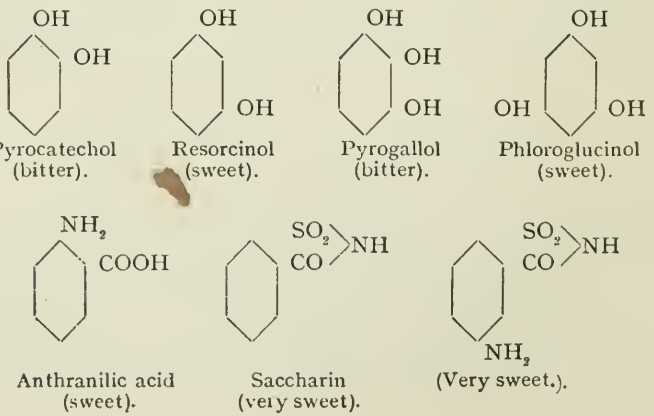
Cacodylic acid is only slightly toxic, and has not the effects of the ordinary arsenic compounds, because it does not ionise. Arsenic and mercury, which induce profound changes in the body, owe their action to the fact of their absorption. Yet arsenic is not much more toxic than iron when the two are introduced into the circulation. In correlation with the marked action of these two metals (arsenic and mercury) is the fact that they are the only two

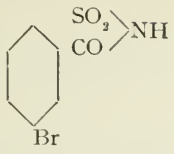
which are to any extent volatile. Also the very great rapidity of absorption of ammonium compounds can be explained by the fact of their volatility. By increasing the solubility of a drug we may (1) render it more toxic by admitting of its easier absorption into the system, but we may also (2) decidedly diminish its activity. Potash salts given by the mouth are non-toxic, because the rate of excretion exceeds that of absorption. Carbolic acid is a very poisonous substance after absorption, but combined with sulphuric acid it is comparatively harmless on account of its rapid excretion, and not because of any alteration in its specific action.

When the constitution of a body is slightly altered, the corresponding change in its action is in many cases directly due to the physical changes, and only indirectly to the change in structure. In other words, the alteration is not due to the drug forming a different type of reaction with the living cell, but to the fact that it is absorbed better, ionises better, penetrates the cell more easily, or to some other altered physical property. It is therefore impossible to draw up general laws forecasting the action of a molecule when it has been subjected to some small change in composition, without knowing the physics of such a change. Thus, hydroxyl derivatives of the aromatic series are said to be antiseptic; amido derivatives, antipyretic; and those which contain an amido group, having one of its atoms replaced by an alkyl group, analgesic. All such statements are futile and based on incorrect supposition. Any exact knowledge regarding the relationship between chemical constitution and pharmacological action is impossible until we know something of the chemical changes going on in the body.

Nevertheless, in spite of these difficulties, we are able to give some examples of allied bodies having a different action, probably in some cases directly due to alteration in the chemical molecules.

If (OH) groups are substituted into the benzene nucleus the action of taste is given to them thus :—





(First sweet, then bitter.) (Very bitter.)

So that the different effects produced on the senses in these cases correspond with differences in the arrangement of the molecule. As a counterblast to such reasoning, however, we should note that dextro-asparagin has a sweetish taste, while lævo-asparagin is tasteless; that dextro-glutaminic acid has a characteristic taste, while lævo-glutaminic acid is tasteless.

As types of the relationship amongst the fatty compounds the following examples are commonly given :—

CH_4	$CH_3.Cl$	$CH_2.Cl_2$	$CH.Cl_3$	CCl_4
Marsh gas.	Methyl chloride.	Methylene dichloride.	Chloroform.	Carbon tetrachloride.

These bodies form a series in which the anæsthetic action becomes greater with the increase in proportion of chlorine. This difference in action is almost certainly largely due to the difference in their physical properties, solubility, volatility, &c. The chlorhydrins afford still another example :—

CH_2OH	CH_2OH	CH_2Cl	CH_2Cl
|	|	|	|
CH_2OH	CH_2OH	CH_2OH	CH_2Cl
|	|	|	|
CH_2OH	CH_2Cl	CH_2Cl	CH_2Cl
Glycerin.	Monochlorhydrin.	Dichlorhydrin.	Trichlorhydrin.

They all depress muscle tissue, and the greater the amount of chlorine the greater the depression.

The fatty alcohols attack the nerve-cells of the brain and cord and produce depression. And we may even formulate a law that the longer the chain (the larger the molecule) the more active they are, until a stage is reached when they are no longer absorbed. The relative toxicity of the more common alcohols is shown in the following table :—

Methyl alcohol*	$CH_3.OH$	Relative toxicity	0.8
Ethyl ,,	$C_2H_5.OH$	,, ,,	1
Propyl ,,	$C_3H_7.OH$	,, ,,	2
Butyl ,,	$C_4H_9.OH$	,, ,,	3
Amyl ,,	$C_5H_{11}.OH$	,, ,,	4

And, again, we believe physical properties which form a parallel series with the chemical composition and physiological action explain the difference in toxicity. No two bodies can be more closely related chemically than the two hyoscyamines (optical

* Immediate effect only is shown here.

isomers), yet some of the most characteristic features in the action of the one are almost entirely wanting in the other.

The following examples do not so readily admit of a physical explanation:—

Ammonia and its compounds produce an excitation of the spinal cord and medulla culminating in convulsions, and they also tend to paralyse motor nerve-endings. If the hydrogen atoms are replaced by alkyl derivatives the action is changed.

$NH_3.H$	$NH_2.C_2H_5$	$N(C_2H_5)_3$
Ammonia (convulsant).	Ethylamine (slightly convulsant).	Tri-ethylamine (non-convulsant).

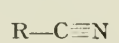
Many of the natural alkaloids are derivatives of ammonia, and if an alkyl group is linked on to this nitrogen the type of action is changed similarly. Thus, to take one example, strychnine in big doses induces convulsions, but methyl-strychnium paralyses the motor nerve-endings like curare, and convulsions are not observed. It suggests an entirely new action, but in reality the strychnine, the methyl-strychnium, and curare, which is also an ammonia derivative, (1) paralyse the motor nerve-endings and (2) induce convulsions. In the case of the methyl-strychnium and curare the convulsions are not observed, because they are masked by the paralysis.

The nitrites owe their activity to the O—N=O group. This group induces relaxation of plain muscle and converts oxyhæmoglobin to methæmoglobin. Amyl nitrite is a typical member of the group, but nitro-pentane, which is an homologous substance, shows

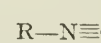
Amyl nitrite.

Nitro-pentane.

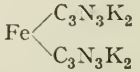
none of the characteristic phenomena. Further examples of this type are afforded by the cyanides. The isocyanides are extremely toxic, as, for example, ordinary potassium cyanide, whilst the



Cyanide or nitrile.



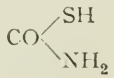
Isocyanide.



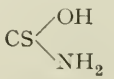
Potassium Ferrocyanide.

nitriles are very much less active. The ferrocyanides are very slightly toxic and pass through the body unchanged. They dissociate into K and FeCy ions, but not into Fe or Cy ions.

The following two bodies show remarkable changes in activity, as a result of converting the sulphur to oxygen atoms:—



Harmless.



Very toxic.

A very large number of substances are now known which exhibit a sympatho-mimetic action—that is, an action of a drug which simulates stimulation of the sympathetic nervous system. The primary amines—butylamine, amylamine, hexylamine—show the effect in a more or less typical manner; in the higher members of the series this effect is complicated by a depressant action on muscle. The aromatic amines which do not possess a phenolic (OH) also exhibit this effect; to produce an optimum action the side-chain of the ring should carry two carbon atoms, of which the second bears the amino group. Of the amines containing one phenolic (OH), the best known is p.-hydroxyphenylethylamine, which is a pressor constituent in putrefying meat and in ergot. The relative action of the amines with two phenolic hydroxyls on the blood-pressure is roughly as tabulated below :—

$(OH)_2C_6H_3$ CO CH_2NH_2	1.5
$(OH)_2$ C_6H_3 CO $CH_2NH.C_2H_5$	2.25
$(OH)_2$ C_6H_3 CO $CH_2NH.C_3H_7$	0.25
$(OH)_2$ C_6H_3 CH_2 CH_2NH_2	1.0
$(OH)_2$ C_6H_3 CH_2 $CH_2NH.CH_3$	5.0
$(OH)_2$ C_6H_3 CH_2 $CH_2NH.C_2H_5$	1.5
$(OH)_2$ C_6H_3 CH_2 $CH_2NH.C_3H_7$	0.25
l$(OH)_2$ C_6H_3 CH(OH) Cu_2NH_2	50
l$(OH)_2$ C_6H_3 CH(OH) $CH_2NH.CH_3$ adrenaline .	35

We believe enough has been said to show something of the difficulty of this problem. (*See also* Local anæsthetics, p. 147.)

CLASSIFICATION

Drugs have been classified in a great variety of ways, chemically, botanically, and physiologically, and even because they possess common physical properties. But no one of these ways is entirely satisfactory. The botanical classification involves the association of aloes and colchicum, of caffeine and quinine, of orange-peel and pilocarpus, none of which have common relationships. A physiological classification is also impossible, because some drugs have two or more important actions, and would have to be ticketed in several places: such a classification would also involve the consideration together of widely different drugs, such as magnesium sulphate and castor oil. A chemical classification is likewise at present impossible, because the chemistry of many of our drugs is not yet known. So we are forced to make an artificial classification, partaking both of the chemical and physiological. Thus, the bodies derived from coal-tar are described together and possess certain actions in common to all. Again, the anthraquinone group of purgatives have a common chemical nucleus and

a similar action ; and conine and nicotine belong to the same group both chemically and pharmacologically. The non-vegetable narcotics form a group possessing no chemical similarities, but having certain common physical properties which we have already mentioned and to which their action is due. The vegetable hypnotics, on the contrary (opium, cannabis indica), possess no chemical or physical relationship, but have a common type of action.

CHEMOTHERAPY

The conception that the protoplasm of the living cell is provided with receptive side-chains to which drugs can attach themselves, and so bring to bear the poisonous properties of a toxophore grouping, is the basis of what is termed chemotherapy. Drugs are supposed to combine chemically with the protoplasm in a way analogous with the binding of toxins—that is, to a receptor which is termed a chemoreceptor to distinguish it from a toxinreceptor.

This idea has led to the search in the laboratory for substances harmful only to infecting parasites causing disease and harmless to their host—that is, for substances which have maximal parasitotropic and minimal organotropic properties. In the beginning it was brilliant with promise, but it is shown elsewhere that no valid evidence obtains for such a conception, and that the value of drugs in parasitic diseases is not due to combination with a side chain on the parasite but to a pharmacological action in which the cells of the host take a prominent part.

Emetine is specific in the treatment of amœbic dysentery, but it only destroys the amœbæ in the animal body: the *Entamœba histolytica* is almost uninfluenced by emetine up to 1 per cent. outside the body. The aniline dyes furnish a clear example of a parasitotropic action; they stain the parasite before the host. Their early promise has not been fulfilled; trypan blue is of value as a remedy for piroplasmosis in domestic animals, but no other success has been recorded; methylene blue has a strong parasiticidal action on spirilla of relapsing fever in the test tube, but fails to act in infected animals.

The organic arsenic compounds are often pointed out as the striking success of chemotherapy, but in the appropriate place it will be shown that they owe their action to their organotropic properties rather than to a direct action on the parasites, such as the spirochætes of syphilis or the trypanosomes of sleeping sickness.

Chemotherapy is thus a speculation based neither on chemistry nor pharmacology.

CHAPTER II

COMPOSITION OF PLANTS

MATERIA MEDICA comprises minerals, plants, and animals. Vital products of plants and animals are not essentially different from compounds which occur in the mineral world; many vital products have been synthesised, examples of such being urea, the uric acid bodies, and the sugars.

The principal groups of substances found in plants and which are employed in medicine are :—

Carbohydrates.—This group includes starches, sugars, inulin, and dextrin. It also contains the gums: these are amorphous carbohydrates, which on addition of water give rise to a sticky solution; such are gum arabic and gum acacia.

Glucosides are bodies which either in the presence of an enzyme or when heated with dilute acid are resolved into two or more substances, one of which is sugar. Thus, the seeds of the bitter almond contain the glucoside amygdalin, which is decomposed in the presence of water by the enzyme emulsin.

$$\underset{\text{Amygdalin.}}{C_{20}H_{27}NO_{11}} + 2\underset{\text{Water.}}{H_2O} = 2\underset{\text{Dextrose.}}{C_6H_{12}O_6} + \underset{\text{Benzaldehyde.}}{C_6H_5.CHO} + \underset{\text{Hydrocyanic acid.}}{HCN}$$

Or, again, sinigrin, the crystalline glucoside found in the horse-radish root, is decomposed by the ferment myrosin, water again being necessary for the change.

$$\underset{\text{Sinigrin.}}{C_{10}H_{16}NS_2KO_9} + \underset{\text{Water.}}{H_2O} = \underset{\text{Allyl isothiocyanite.}}{C_3H_5.NSC} + \underset{\text{Dextrose.}}{C_6H_{12}O_6} + \underset{\text{Acid potassium sulphate.}}{KHSO_4}$$

As further examples, we have salicin, a crystalline glucoside from willows and poplars, the glucosides from digitalis and other drugs allied thereto; and arbutin, which is decomposed by the fungus aspergillus with the liberation of quinol.

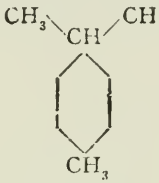
Saponin is the name given to a group of bodies, generally glucosides, which froth when mixed with water and possess the general formula $C_nH_{2n-8}O_{10}$. In quillaia bark two such bodies, "sapotoxin" and "quillaic acid," are present, and are identical with two other

substances present in senega root. It is probable that most saponins contain the quinol complex.

Fixed Oils and Fats are mixtures of non-volatile compounds of fatty acids and glycerine. The more common fats are :—

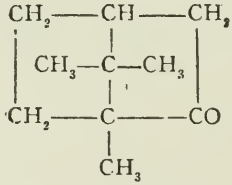
$C_3H_5(C_{16}H_{31}O_2)_3$ Palmitin. $C_3H_5(C_{15}H_{35}O_2)_3$ Stearin. $C_3H_5(C_{15}H_{33}O_2)_3$ Olein.

Volatile or Essential Oils give the characteristic odour and taste to plants. They are complex mixtures of various substances, the three most important members being termed pinene, camphene, and limonene, and are classed together as the terpenes ($C_{10}H_{16}$). The terpenes are closely related to cymene, a body which is found in some of these oils—for example, in oil of eucalyptus.



Cymene.

Stearoptenes are crystalline oxidised hydrocarbons, or solid volatile oils. There are three in the Pharmacopœia: camphor, menthol, and thymol.

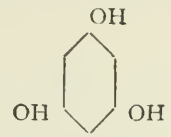


Camphor.

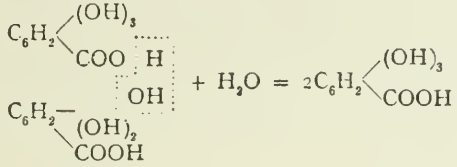
Resins are complex mixtures insoluble in water, but soluble in alcohol. When they are dissolved in essential oils they form oleo-resins, such as copaiba and turpentine, and when with gums, gum-resins, ammoniacum, asafœtida, galbanum, and myrrh. Pine resin is the residue which is left after distilling the volatile oil from turpentine ; it contains nearly 90 per cent. of the anhydride of abietic acid. All resins are insoluble in water, but are soluble in alkalies and spirit. Typical resins are those of guaiacum, jalap, scammony, and podophyllum.

Tannins are a large group of bodies possessing a benzene nucleus : they have an astringent taste, and combine with proteins and gelatine, forming an insoluble compound, leather. They are all more or less soluble in water and alcohol, and precipitate alkaloids from solution. They form a characteristic dark-blue or black colour with iron salts (ink). The tannins are easily broken up, some yielding glucose and others resinous substances or pyrocatechin. Many

of the tannins—for example, those from kino catechu and horse-chestnut—contain the phloro-glucin complex.



Tannic acid from oak-galls is not a glucoside, but a condensation product of two molecules of gallic acid. Hydrolysis is readily produced by boiling with a little acid, thus :—

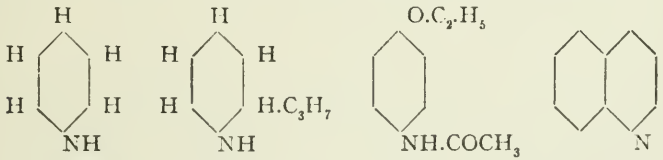


Tannin. Gallic acid.

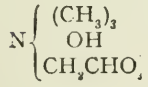
Alkaloids are basic organic substances, usually vegetable in origin, and having an alkaline reaction ; like alkalies, they combine with acids to form salts. The pure alkaloid is usually insoluble in water, but is soluble in such solvents as chloroform, ether, or petroleum. The salts of the alkaloids are, on the contrary, quite soluble in water or alcohol.

Leucomaines and ptomaines or animal alkaloids possess many chemical and physiological properties similar to the vegetable alkaloids ; they may be formed either normally as a vital physiological process, as adrenalin and creatinine, or as the results of putrefaction, as cadaverine. Sometimes they are responsible for poisoning by food : for example, decomposition of cheese, milk, or cream gives rise to a poison tyrotoxicon (diazo-benzene butyrate). Many of the vegetable alkaloids possess a pyridine or quinoline nucleus.

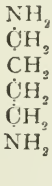
The following may be regarded as examples of alkaloids :—



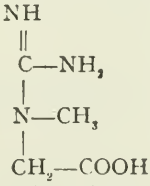
Piperidine. Coniine. Phenacetine. Quinoline.



Muscarine.



Putrescine (decomposition of animal matter).



Kreatine (in normal muscle).

Proteins.—Several proteins of animal origin are poisonous, such, for example, as the snake venoms. Like other proteins they are destroyed by ferments, and are, therefore, harmless when taken by the mouth.

In plants we have somewhat allied substances in ricin and abrin, which are extremely poisonous and are obtained from the castor-oil seed and jequirity bean respectively.

Neutral Principles are bodies having a complicated chemical constitution, an action resembling that of the alkaloids, and not giving the ordinary alkaloidal reactions. Such are elaterin, chrysarobin, cantharidin, and santonin.

Other Substances.—Besides the bodies named, plants contain other substances of little medicinal value, such as the various colouring matters, bitter principles whose only physiological action is the bitter taste, alcohols, acids, aldehydes, &c.

PREPARATIONS USED IN MEDICINE

The Pharmacopœia contains a list of the preparations of the various crude drugs, as well as their method of preparation. The physician of the past used many drugs in his prescriptions, all mixed up together and forming a mass of organic matter, the effect of which it would be almost impossible to foresee. To-day the physician is content to use one or two at a time.

Crude drugs are employed still when the pure active constituent might be advantageously substituted. The action of strychnine is clearly defined, its solubility and rate of absorption have been accurately determined, whereas of nux vomica, the crude bean from which strychnine is obtained, little is known; its rate of absorption has not been examined, and the effects of the other ingredients are not clearly determined. If we prescribe this drug we cannot tell how much brucine we are giving, for the ratio of strychnine to brucine may vary as much as from 3 : 1 and 1 : 2 respectively.

The only scientific procedure is to prescribe the alkaloid, and all the preparations containing nux vomica might with advantage be eliminated from the Pharmacopœia. This is only one example of many cases where crude drugs are still employed, and in which a pure alkaloid might be substituted with every advantage.

The principal solvents employed in the Pharmacopœia are the following :—

(1) *Water.*—As in the waters, liquors, infusions, decoctions, mixtures, and syrups.

(2) *Alcohol.*—Advantageous for resins, volatile oils, glucosides, alkaloids, and neutral principles. Such preparations keep indefinitely, and are, therefore, different from decoctions and infusions, which should be prepared fresh. Alcoholic preparations are the tinctures, spirits, wines, and some of the liquors.

(3) *Glycerine.*
(4) *Collodium.*
(5) *Olive Oil.*

The following are the methods of preparing the crude drugs in a suitable form for administration:—

Aquæ.—Prepared by distilling the drug with water and preserving the distillate. Aq. camphoræ and Aq. chloroformi are, however, obtained by simple solution. Their dose is 1 to 2 oz. or more. Aq. laurocerasi is an exception, and its dose is only up to 2 drs., since it contains 0.1 per cent. hydrocyanic acid.

Decocta.—Decoctions are preparations obtained by boiling the drugs in a suitable state of division with distilled water in a covered vessel for a fixed time, generally about ten minutes, and then straining. Dose ½ to 2 oz.

Infusa.—Infusions are obtained by treating the prepared drug with boiling water and straining. Calumba and Quassia are made with cold water. The time of maceration with the water varies. Dose ½ to 1 oz. Infusion of digitalis 2 to 4 drs. Infusions of ergot, lupulus, and scoparium may be given up to 2 oz.

Tincturæ.—Tinctures are preparations obtained by dissolving out the constituents of a crude drug by alcohol. For this purpose two strengths of alcohol are employed in the British Pharmacopœia: rectified spirit, 84 per cent. alcohol by weight, and proof spirit, 49 per cent. by weight.

Some tinctures are prepared by a simple solution of the drug in spirit, others by maceration only, and others again by maceration with a portion of the alcohol for forty-eight hours, followed by percolation with the remainder.

Spiritus.—Spirits are mostly solutions of volatile oils in rectified spirit.

Vina.—Wines resemble tinctures in their mode of preparation, but sherry or orange wine is substituted for alcohol.

Succi consist of the juices expressed from fresh plants and preserved by adding rectified spirit. They are principally used to flavour.

Linimenta are preparations which have an oily, soapy, or alcoholic basis, and are intended for external application accompanied by friction.

Misturæ (Mixtures) are fluid preparations in a suitable form for administration, and having a dose of ½ to 2 oz.

Liquores are solutions of different chemical substances in water. Many are prepared by complex processes.

Extracta may be solid or liquid. Solid extracta are prepared by exhausting the drug by maceration or percolation with a suitable menstruum, the bulk of which is subsequently removed by evaporation. In the case of fluid extracts the evaporation is not carried so far and rectified spirit is added to preserve the fluid from decomposition.

Mella, or preparations of honey.

Lotiones are liquid preparations for external use.

Pulveres, powders. Prepared by mixing ingredients and passing them through a fine sieve. Dose variable, generally up to about 40 grains.

Pilulæ (pills).—The constituents are well mixed together in a mortar; then kneaded into a firm mass with a suitable excipient, and made into the size and form desired by a pill machine.

Olea.—Oils are of two kinds:—(1) The **fixed,** composed chiefly of esters of certain fatty acids and obtained by expression; and (2) the **volatile** or essential oils, composed chiefly of substances belonging to the benzene series, and are the products of distillation. Dose ½ to 3 m. unless otherwise stated.

Mucilagines are watery solutions of a gum. Two are official:—Mucilago acaciæ and mucilago tragacanthæ.

Unguenta.—Ointments are preparations having a fatty basis and intended for external application. The bases generally employed in the British Pharmacopœia are:—

(1) Paraffin, a mixture of hard and soft.

(2) Lard, which is more readily absorbed by the skin than paraffin.

(3) Wool-fat, perhaps the most readily absorbed.

Watery solutions of drugs are not absorbed by the skin since they cannot penetrate the fatty constituents of the glands. Ointments, however, if rubbed in (inunction), are absorbed and carry the drugs with them. Mercury is often given this way.

Glycerina.—Solutions of various drugs in glycerine.

Injectiones Hypodermicæ.—Fluid preparations employed for injection. The vehicle is boiled and cooled before the drug is dissolved.

Syrupi consist of a strong solution of refined sugar in distilled water. The medicinal agent is generally added in a state of solution. Their value consists in their being palatable, and the fact that the sugar behaves as a preservative and retards chemical changes. The dose averages a drachm.

Suppositoria.—Solid bodies having a conical shape and weighing about 15 grs. intended for introduction into the rectum. They generally have a basis of theobroma (cocoa fat).

Confectiones are preparations having a basis of sugar or honey of the consistence of a thick paste. Dose 60 to 120 grs.

Enemata are fluid preparations for injection into the rectum. They resemble the misturæ in their mode of preparation.

Tabellæ (tablets). Only one preparation is official:—

Tabellæ trinitrini (tablets of chocolate each weighing 5 grs., containing 0.5 milligram of trinitroglycerin).

Collodia.—Pyroxylin dissolved in a mixture of ether and alcohol:—

Collodium, collodium flexile, collodium vesicans (contains blistering liquid).

Trochisci (lozenges) are prepared by incorporating the medicinal agent with refined sugar and powdered gum acacia, and heating in an oven. They are principally used in diseases of the mouth and pharynx and for children.

Emplastra are solid adhesive applications for external use. They are used for support or for applying remedies externally.

Patent Medicines should, according to the law, comply with two requirements: First, they should be an original invention; and, secondly, a complete description of them must be filed at the Patent Office so as to be accessible to the public.

It need hardly be pointed out that the majority of the so-called patent medicines are not so in the legal sense: they would be better defined as secret remedies.

The following list gives the ingredients of some of these preparations :—

Aperient and Liver Pills

Beecham's Pills.—Aloes, ginger, and soap.

Bile Beans.—Cascara, rhubarb, liquorice, and oil of peppermint, coated with gelatine.

Cockle's Pills and Barclay's Pills.—Aloes, colocynth, and rhubarb.

Carter's Little Liver Pills.—Podophyllin ($\frac{1}{8}$ gr.) and aloes soc. ($\frac{1}{3}$ gr.) in each pill.

Holloway's Pills.—Aloes, rhubarb, saffron, Glauber's salts, and pepper.

Scott's Pills.—Aloin and cascara, with a soap basis.

Saline Aperients

Eno's Fruit Salt.—Bicarbonate of soda, tartaric acid, and citric acid.

Lamplough's Pyretic Saline.—Citric acid with bicarbonate of potassium and sodium.

Cough Mixtures and Lozenges

Keating's Cough Lozenges.—Ipecacuanha, lactucaria, squill, liquorice, tragacanth, and sugar.

Owbridge's Lung Tonic.—Ipecacuanha, oil of aniseed, and oil of peppermint.

Preparations for Gout and Rheumatism

Eade's Pills.—Salicylate of sodium, guaiacum, and aloes.

Blair's Gout Pills.—The active ingredient is colchicum.

Preparations for Headache and Neuralgia

Antikamnia.—Bicarbonate of sodium, antifebrin, and caffeine.

Bromidia.—Bromide of potassium, chloral, hyoscyamus, cannabis indica, oil of aniseed, syrup and water.

Preparations for Asthma

Crevoisier's.—Belladonna, foxglove, stramonium, sage, and nitrate of potassium in equal parts.

Plant's Cigarettes.—Leaves of stramonium, lobelia, and green tea.

Miscellaneous Preparations

Doan's (Back-ache) Pills.—(1) White-coated aperient (dinner pills): Podophyllin, aloin, jalap, and peppermint. (2) Brown-coated (back-ache pills): Oil of juniper and hemlock pitch.

Guy's Tonic.—Phosphoric acid, tincture of cochineal, infusion of gentian, and chloroform water.

Chlorodyne.—Chloroform, ether, hydrocyanic acid, morphine, cannabis indica, capsicum, peppermint, and treacle.

Clarke's Blood Mixture.—The active constituent is iodide of potassium (about 6 grs. to the ounce).

Pink Pills.—Sulphate of iron, an alkaline carbonate, and liquorice, thickly coated with sugar, and coloured with carmine.

Phosferine.—Quinine, phosphates, and hypophosphites.

Seigel's Syrup.—Aloes, capsicum, liquorice, and treacle.

Steedman's Teething Powders.—Calomel and starch.

Capsuloids.—Hæmoglobin, olive oil, oleic acid, and balsam of Peru.

Antipon.—A solution of citric acid in water with a little red colouring matter.

Incompatibility.—Certain remedies may not be prescribed together either for chemical, pharmacological, or physical reasons. As regards the first, a sufficient knowledge of chemistry should have been attained to avoid errors of this type. Examples of chemical incompatibility are :—

(1) Precipitation as by prescribing together sodium carbonate and sulphate of iron.

(2) Decomposition by acids or alkalies such as

$$Na_2CO_3 + 2HCl = 2NaCl + CO_2 + H_2O.$$
$$(NH_4)_2CO_3 + 2KHO = K_2CO_3 + 2H_2O + 2NH_3.$$

(3) Precipitation of alkaloids as by adding sodium carbonate to a solution of morphine.

(4) The liberation of free iodine as with potassium iodide and nitrous ether.

(5) Tannin and iron.

It is better to prescribe potassium permanganate, potassium iodide, tannic acid, and mercuric chloride alone. Physical incompatibles are such mixtures as olive oil and water or magnesium sulphate and an excess of alkaline tincture.

STANDARDISATION OF DRUGS

The plants used in medicine cannot always be grown under the same conditions. The soil, season, gathering time, drainage, are a few of the variables ; and it could hardly be anticipated that the amount of active constituent found, say, in the leaf of a plant would be constant under all these conditions. It is found that the percentage of active constituent varies greatly, and without any corresponding variation in the appearance of the plant. For this reason it was decided to standardise drugs. It was first suggested that this should be done by estimating the total extractive matter which could be obtained with some definite solvent. This method was found useless, since the percentage of active principle to extractive shows the widest variations ; consequently it was

decided that the active principle must be determined. The Pharmacopœia demands that certain preparations of opium, belladonna, nux vomica, and cinchona shall contain a certain percentage of total alkaloid, and that ipecacuanha, jalap, and cherry-laurel water shall have their active constituents standardised. Now this is certainly a move in the right direction, but more remains to be done. Two examples will explain this: Opium, a sleep-inducing substance, is required by the British Pharmacopœia to contain about 10 per cent. morphine; but this drug also contains other alkaloids, and particularly narcotine, which may be present in any amount from 2 to 10 per cent. Now narcotine tends to produce convulsions, and in certain preparations and conditions its effects may overshadow those of the morphine. All such difficulties may be avoided by prescribing the active principle instead of the crude preparation of the plant. It is true that a few authorities still assert that the whole action of the plant is not represented by any one active constituent, and this is no doubt true; but it must be remembered that we know in most cases the pharmacology of the active constituent, but not of the crude drug. How the wax, oil, fat, resin and tannin, &c., affect the absorption and otherwise influence the action of the drug it is not always easy to say. As time goes on we shall find that these crude preparations will tend more and more to drop out from practical therapeutics, and in their place the pure crystalline alkaloids will be substituted. This has already been accomplished for some drugs; quinine, for example, almost entirely supersedes the employment of cinchona bark.

There are several drugs, particularly those containing glucosides, which it is impracticable to standardise by the ordinary methods on account of the difficulty or impossibility of preparing an active principle; yet these are at least as important in medicine as those which are standardised. It has been shown, for example, that the strength of various samples of digitalis (foxglove) varies enormously, and the different so-called active principles extracted from the plant vary even more than the crude preparations. Some of these principles are very poisonous and some entirely inactive, so that they require standardising much more than the crude preparations; and, of course, the total amount of glucoside present in a specimen is of no value as an indication of its activity.

It is extremely important that these drugs should be standardised, and so a new method of effecting this has been introduced, namely, to measure their activity on animals. What pharmacology already owes to experiments on animals has been pointed out, as well as the fact that the type of action of any one drug having a specific effect is the same in all the mammalia. So it has been suggested that ergot, digitalis, strophanthus, squill, and Indian hemp should be assayed by this method. Of course, it is not suggested that a dose determined for an animal should be at once referable to man by a simple proportion, viz. the relative weights of the man and

animal. But a simple relationship between the dose necessary to affect an animal and a man respectively having been once estimated, in all future experiments the animal simply serves as a test by means of which the activity of the drug is determined. It is not justifiable to determine the activity of, say, a digitalis preparation on a patient, so that standardisation on animals is the only method which is open to us. The method is not so unusual as it may at first appear, for the British Pharmacopœia suggests as one of the tests for atropine its instillation into the conjunctiva. Further, who would care to employ an antitoxin of unknown strength? It is just as essential to standardise digitalis as it is to standardise antitoxin.

The preparations of digitalis, strophanthus, and squill, which are all members of a group of drugs which have a specific affinity for cardiac muscle, may be standardised in a variety of ways. First, they may be tried on the frog's heart; for this purpose all kinds of precautions are necessary: there must be no abnormal conditions such as spawning, the frog should be of a definite size, and the drug must be given always under precisely the same conditions. This method is sufficiently accurate. These drugs may be standardised more accurately by perfusing the isolated rabbit's heart with Ringer's solution, and subsequently adding the drug.

Ergot affords another example of a drug which it is absolutely necessary to standardise. Fowls form a sensitive reagent for this purpose, as after a certain amount of the drug the comb and wattles become gangrenous and drop off. Indian hemp may be mentioned as a last example. The active constituent of this drug varies enormously with the place in which the plant is grown, the season, the time it has been kept, exposure, while many of the specimens on the market are valueless. It is best assayed by injecting the preparation into either dogs or cats. The animals after initial stimulation become narcotised.

The Pharmacopœia directs that the following drugs be standardised:—

Extractum opii (20 per cent. morphine), extractum opii liquidum (0.75 per cent. morphine), tinctura opii (1 per cent. morphine), extractum nucis vomicæ siccum (5 per cent. strychnine), extractum nucis vomicæ liquidum (1.5 per cent. strychnine), tinctura nucis vomicæ (0.125 per cent. strychnine), extractum belladonnæ siccum (1 per cent. total alkaloid), extractum belladonnæ liquidum (0.75 per cent. total alkaloid), tinctura belladonnæ (0.035 per cent. total alkaloid), emplastrum belladonnæ (0.25 per cent. total alkaloid), linimentum belladonnæ (0.37 per cent. total alkaloid), unguentum belladonnæ (0.6 per cent. total alkaloid), extractum cinchonæ liquidum (5 per cent. total alkaloid), tinctura cinchonæ (1 per cent. total alkaloid), tinctura cinchonæ composita (0.5 per cent. total alkaloid), acetum ipecacuanhæ (0.1 per cent. total alkaloid), extractum ipecacuanhæ liquidum (2.0 to 2.5 per cent. total alkaloid), vinum ipecacuanhæ (0.1 per cent. total alkaloid), aqua laurocerasi (0.1 per cent. HCN).

THE MODE OF ADMINISTRATION OF DRUGS

The action of a drug may vary considerably according to the method in which it is administered. Adrenaline taken by the mouth has a local action on the stomach only, but injected intravenously it produces an enormous rise in the blood-pressure; a dose of saponin which is harmless when given by the mouth, gives rise to poisonous symptoms if injected under the skin.

Drugs are used for their local action principally on the skin, eye, the mucous membranes of the alimentary, respiratory, and genito-urinary tracts. Poultices, plasters, blisters, ointments, collodions, caustics are used to produce a direct **local action** on the skin. Gargles and lozenges are employed for their local effect on the pharynx and tonsils; but it is necessary to remember that gargling does not affect the tonsils directly, since the fluid used does not come in contact with them. The respiratory tract may be influenced locally by the inhalation of vapours. Injections are employed for their local effect on the genito-urinary tract and on the nose. The eye is especially the organ which calls for local treatment, sometimes for the purely local action of the drug, as, for example, the use of mercury as a disinfectant, and sometimes for the special action of the drug on the pupil after local absorption. And, lastly, drugs may be applied to the rectum in the form of a suppository or enema either for their local action or for absorption into the system.

Drugs are used in a variety of ways to produce a general effect. The usual method of prescribing them is by the **mouth,** but even by this method they are sometimes employed for their local action on the stomach—for example, bismuth and emetics; or for their local action on the intestines (vegetable purges). They are, however, generally given by the mouth to produce their specific effects after absorption.

Hypodermic Injection.—This method of employing drugs is also occasionally used for their local action; cocaine, for example, may be injected to produce local anæsthesia before conducting minor operations.

The method has the objection that it may be painful if an irritant substance is used. But its advantages are great, since the absorption of all the drug is ensured; at the same time, the effect is obtained more quickly, although it does not last so long as if the drug is given by the mouth. A further advantage is that local action on the alimentary canal is avoided. The fluid to be injected should be free from micro-organisms and non-irritant, and the dose about half that given by the mouth.

Occasionally when a drug is irritant a deep or intra-muscular injection may be made: mercury is sometimes used in this way in the treatment of syphilis.

Intravenous Injection.—Drugs administered in this way

immediately become active, and their maximum effect is attained a few seconds after injection. The drug, as a rule, is also excreted rapidly, so that the action is powerful but short; it may be employed, for example, during a paroxysm of malaria when quinine is injected to abort the attack. All drugs do not produce their effects immediately after injection into the blood. This holds true for the metals as a whole, for colchicine, and for toxins and antitoxins. An explanation of this delayed action will be considered later.

Rectum.—Drugs are often administered by the rectum for absorption into the system, especially when it is desired to avoid a local effect on the stomach; this is not infrequently the case with morphine.

Some drugs of a volatile nature—for example, chloroform, ether and amyl nitrite, oxygen and nitrous oxide—are usually administered by **inhalation** to produce their specific effects.

ABSORPTION

Most drugs are given with the object that they may be absorbed into the blood-stream and so give rise to their specific effects. Drugs may be applied to the skin with this object; but here, in order that the drug may be absorbed, it must pass through either a sebaceous or sweat gland, since absorption through the horny epithelium is impossible. Now the cutaneous glands are filled with fatty material to which water is impervious, and hence the drug, which it is desired should be absorbed, must be dissolved either in fatty substances or in alcohol, all of which find their way through the fat: hence, cod liver oil, if rubbed into the skin, produces its ordinary effect. Inunctions of this type are also used for mercury, as by this means the direct action of the metal on the stomach and intestines is avoided. In the same way, alkaloids and other active substances, provided they are dissolved in oily preparations, may be absorbed through the skin, as by this means they come into contact with the living bioplasm of the glands, by which they are taken up into the system.

When drugs are applied to the conjunctiva of one eye they diffuse and are absorbed locally, and affect the physiological mechanism of this eye to a very decided degree. By the time the drug has been absorbed into the general circulation it is so diluted as to produce little or no effect on the opposite eye. It is known that if strychnine is injected subcutaneously in the region of the temple it affects the eye of the same side (increasing the acuteness and enlarging the field of vision) before that of the opposite side. And it can be shown by chemical tests that such substances as potassium iodide, sodium salicylate, and potassium ferrocyanide, when injected into the temporal region of an anæsthetised dog, find their way into the orbital cavity of the near eye several minutes before they can be

detected in the opposite eye. The drug must, therefore, be conducted at first by local diffusion, not by the blood-current.

An obsolete method for promoting absorption of drugs from the skin is known as the endermic. It consists in first removing the epithelium with a blister and then applying the drug.

When drugs are administered by the mouth they are absorbed principally by the upper portion of the small intestine, the stomach and œsophagus being almost inert in this respect. An experiment to show the relative amount of a drug absorbed in different parts of the alimentary canal may be made by injecting a known quantity of a drug, whose symptoms are easily recognised, such, for example, as strychnine, which produces convulsions, into ligatured portions of the alimentary tract of an anæsthetised animal. The time between this injection and the onset of convulsions represents, roughly, the time of absorption of a definite quantity of the drug. The following table shows the results so obtained:—

Stomach.	Injection	1½	grs.	strychnine.	Convulsions in	30 minutes.
Small intestine	,,	,,	,,	,,	,, 10	,,
Œsophagus	,,	,,	,,	,,	,, 50	,,
Colon	,,	,,	,,	,,	,, 14	,,
Rectum	,,	,,	,,	,,	,, 7	,,

So that the isolated rectum absorbs at least as well as the small intestine.

From the stomach most drugs under ordinary conditions are absorbed very slowly, but some, particularly alcohol, are taken into the system rapidly. Alcohol is not only absorbed rapidly, but it decidedly accelerates the absorption of other bodies dissolved in it.

The absorption from both the stomach and intestines is influenced by the amount of food present. In some cases the food enters into combination with the drug: this, for example, is the case with tannin, which combines with some of the albumen in the food and forms an insoluble tannate of albumen, a body analogous to leather, whereas, if the stomach is quite empty, the tannin may produce an irritant effect on the epithelium, and even penetrate the superficial part of the cells, inducing vomiting. Absorption also depends on the form in which the drug is administered: the gums and resins in tinctures and extracts tend to prevent absorption. After the administration of such preparations absorption may be delayed for so long a time that the active constituent, or a large amount of it, which when administered alone is rapidly absorbed, is excreted through the fæces unchanged without passing into the circulation. Volatility is another factor which influences absorption. For example, the volatile oils are the better antiseptics because their volatile properties allow them to enter the substance of bacteria the more readily. The great rapidity with which hydrocyanic acid gets into the system is largely dependent on volatility. The mechanism by which the mucous membrane of

the alimentary canal allows the ready absorption of some substances and prohibits the absorption of others is unknown. Why are the K and Cl ions absorbed so easily when the SO_4 and Mg ions are hardly absorbed at all? The explanation may possibly be determined by the influence of the various substances on the colloidal arrangement in the cells of the mucous membrane. And certain it is that the presence in the alimentary canal of non-absorbable substances hinders the absorption of other substances: thus the effect of strychnine injected into a loop of intestine of an anæsthetised animal is considerably delayed by the presence of magnesium sulphate.

Most drugs on reaching the blood exert their specific effects immediately on some special tissue, but there are a few exceptions, such as the toxins. As a special example, tetanus toxin may be mentioned; this is absorbed by the cells of the central nervous system by way of the peripheral nerve-trunks independently of the paths of blood and lymph. Tetanus toxin circulating in the blood has no immediate action on the nerve-cells. The neurones are protected from the poison, and the toxin can only reach them by the long path of the axis cylinder process after its absorption at the motor nerve-endings in the muscle. After absorption drugs pass to the liver, many are here changed chemically, such as the salicylates, whilst others are for a time retained, such as iron.

Finally, it must be remembered that very many drugs are either not absorbed at all or only in minute amounts. Of the common metals, the only two which are at all readily absorbed are those which are volatile (arsenic and mercury), and the absorption of the others is so slow that weeks or months of ingestion may be required to induce poisoning. An injection into the circulation of equal amounts of arsenic and iron is attended with almost equally serious results. The difference in toxicity is largely a question of absorption, and arsenic and mercury are more poisonous than the other metals because they are more easily absorbed. Again, the saponins, a group of drugs used to excite expectoration, are not absorbed, and their action is mainly due to some irritation of the alimentary canal which induces reflex effects on the respiratory tract. Yet if saponins are injected into the circulation they produce serious symptoms. Purgative drugs should not be absorbed, and, indeed, this is one essential of an ideal purgative. Hence it is not advisable to prescribe a purgative drug as a pure crystalline active principle, since in this form absorption is facilitated; it is much better to prescribe the crude drug.

CHAPTER III

ALCOHOL

Absolute alcohol consists of ethyl hydroxide, C_2H_5OH, and should not contain more than 1 per cent. by weight of water. The amount of alcohol present in the more common beverages is shown in the following table:—

Brandy	35 to 50 per cent.
Sherry	12 to 18 ,,
Claret	10 ,,
Public-house beer	5 ,,
Pilsener lager	3·3 ,,

The percentage in spirits (brandy, whisky, and rum) is fixed by the law in this country at 25 per cent. under proof, *i.e.* about 36 per cent. alcohol. Beer is a fermented sugar infusion containing a bitter. The best material for fermentation is malt, but glucose prepared from rice or potato is often used. Hops form the best bitter. Wines are produced by the fermentation of grape juice, and the alcohol so formed never exceeds 13 per cent., as the growth of the yeast is then arrested. During the maturing of the wine by age mixed ethers are formed which modify the action of the alcohol. Brandy is obtained by the distillation of wine, and it necessarily contains a greater concentration of these more volatile ethers. Cheap brandy is often made by flavouring grain spirit. Gin is grain spirit to which oil of juniper, coriander seeds, &c., are added, and the whole then redistilled. Whisky is distilled from fermented malt or grain. When freshly prepared it often contains deleterious substances such as fusel oil, which gradually disappear with age. Most of the "whisky of commerce" is prepared from alcohol which is flavoured by keeping in a sherry cask—the so-called patent-still spirit.

Alcohol is prepared by fermenting grape sugar with yeast.

$$\underset{\text{Glucose.}}{C_6H_{12}O_6} = \underset{\text{Alcohol.}}{2C_2H_5OH} + \underset{\text{Carbon dioxide.}}{2CO_2}$$

This change is brought about by a non-organised ferment, "zymase," which can be obtained by pressure from the yeast cells and which

is analogous to the various ferments which, in late years, have been extracted from intra-cellular juices.

External.—The action of alcohol on the skin depends upon (1) its volatility, and (2) its power of absorbing water and precipitating proteins. As a result of the former action the part to which it is applied is cooled, and as a result of the latter hardening of the tissues is induced. If it is applied to the skin and prevented from evaporating, or if it is rubbed into the skin, there is a **rubefacient** effect, *i.e.* local vaso-dilatation. Alcohol is also employed as an antiseptic.

Sodium ethylate (C_2H_5ONa), a body prepared from alcohol, is used as a mild caustic for warts and small growths.

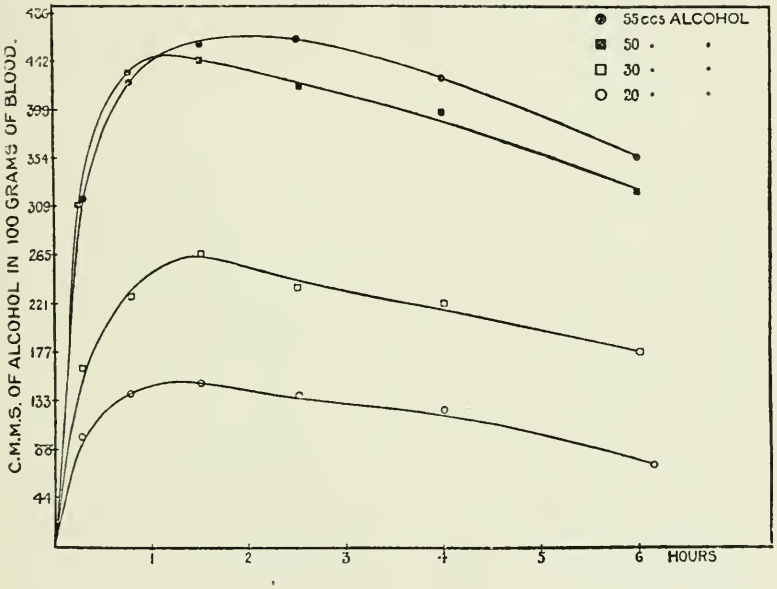
Action on the Mouth and Stomach.—Alcohol even up to 5 per cent. does not influence the digestive power of ferments outside the body. Larger amounts have a retarding action. By the direct contact of alcohol with the mouth a slight stimulation of salivary secretion is brought about, which is characterised by a greater digestive power over farinaceous food than ordinary saliva: the effect is reflex, and only obtained by direct contact of the alcohol with the buccal mucous membrane and not by circulating alcohol.

Alcohol augments the flow of gastric juice; this is produced mainly by the direct local action of the drug on the gastric mucous membrane, but not entirely, since the flow is still augmented a little if the alcohol is absorbed from the small intestine. The difference between the action of alcohol and food on the stomach should be carefully distinguished. The former simply augments the flow of juice, and does not induce the cells to secrete an active ferment. For example, supposing alcohol is administered during starvation when the gastric cells are free from pepsin, the resultant juice, though containing an abundance of hydrochloric acid, does not convert proteins into peptones.

Alcohol in small amounts slightly accelerates the digestion of proteins. It is very rapidly absorbed from the stomach. For example, 200 c.c. of a 37 per cent. solution of alcohol was placed in the stomach of a dog in which the pylorus had been ligatured; absorption was complete in about three hours. Alcohol hastens the absorption of bodies which are administered dissolved in it, and this property is occasionally made use of in the administration of drugs. The flow of pancreatic juice is somewhat increased as a result of the augmented flow of hydrochloric acid from the stomach which converts the pro-secretin in the cells of the upper part of the small intestine into secretin; the latter is absorbed and excites the pancreas.

When alcohol is taken by the mouth a maximal concentration occurs in the blood and tissues in about half an hour: this concentration is, within moderate limits, proportional to the amount

taken. The disappearance of the alcohol from the blood and tissues is very slow: it is not burned off like a wet squib, but is used up apparently like sugar, the tissues destroying 0 185 c.c. per kilo body-weight per hour. Alcohol produces the same maximal concentration in the blood, whether it is taken in a single dose or in two or three doses at intervals within two hours; that is, it accumulates for the time on account of its slow destruction. The absorption of alcohol is facilitated by drinking water some hours previously on an empty stomach, and is delayed by the presence of foods, especially fats, in the stomach.



Dog. Wt. 13 Kilos.

Shows the varying of alcohol in the blood according to the amount taken. Note the slow rate of destruction. (Mellanby.)

Action on the Central Nervous System.—Alcohol even in small doses has a pronounced action on the central nervous system. It gives rise to a general feeling of well-being, with a lack of regard for scruples; and the consequences of action are apt to be left unconsidered. The subject becomes more reflex, more self-confident, and less shy. At the same time he exhibits less self-control, and the emotional side of his character becomes very pronounced; for example, the jovial man becomes hilarious, the choleric pugnacious, and the melancholic lachrymose. People

so influenced exhibit an excess of motor energy, all their movements seem to be more lively but to lack their natural dignity. The patient is convinced of the brilliancy of his thoughts and expressions; he is no longer at a loss for words, and is ready to give his dictum on all subjects. This "brilliancy" is, however, a self-deception; the observant onlooker notes that expressions and words are ill-chosen, and that the sparkling conversation will not bear analysis. Nevertheless, these effects have, naturally enough, given rise to the popular conception that alcohol is a valuable cerebral stimulant.

With large amounts of alcohol there is a second or paralytic stage in which the psychical phenomena become more pronounced and all the sensations blunted; speech is thick and muttering, and the movements ungainly. This condition is followed by stupor and sleep, which gradually pass into unconsciousness and coma, death ensuing from respiratory paralysis.

Mode of Action.—Before considering the mode of action it is necessary, in the first place, to be perfectly clear that alcohol excites certain parts of the central nervous system. This is shown by the fact that after a small dose certain mental operations are shortened.* Simple reaction time is at first quickened, simple mental associations, such as making words to rhyme, are performed more rapidly, and some elementary efforts, such as reading in a whisper, are facilitated. Further, small differences in weights, as shown by Jacobi, are estimated more accurately; and besides these, evidence has already been given to show that the motor area of the cortex is in a condition of hyperexcitability.

The facts which we have set forth here may be explained in one of two ways. The first theory may be regarded as that of Binz, who believed that alcohol first stimulated the nerve-cells in the central nervous system, and later depressed them. He drew attention to all the facts which we have mentioned already, and further gives some evidence of stimulation of the medulla, which will be considered under respiration.

The second theory is that of Schmiedeberg. His school claims that alcohol does not exert any direct stimulant action on the central nervous system, but that on the contrary it depresses from the beginning. The depression follows an evolutionary order, picking out those centres first which are developed last; thus the finer degrees of attention, judgment, and perception are among the first to go. So the depression follows the inverse order of evolution until at last the medulla is paralysed: this process is spoken of as dissolution. The stimulation effects, already described, are accounted for in this theory by the depression of the inhibitory centres. The man becomes more reflex, loses his fear of consequences, his shyness and self-control. We have an explanation of "Dutch courage,"

* Greater brevity of cerebral time is here assumed to be the result of stimulation.

and the "brilliance" of the after-dinner speaker. The motor excitement can be explained in the same manner.

The direct evidence in support of this theory is remarkably imposing, and points to the fact that such quantities of alcohol do not increase the quantity or vigour of mental opinions, but tend to lessen the power of clear and consecutive reasoning.

It has been shown by many observers that attention, judgment, and the higher mental processes are retarded at once by amounts of alcohol insufficient to intoxicate. Thus Kraepelin showed that whilst simple motor processes are at first accelerated, psychical processes, such as arithmetical problems or reaction times involving choice, are never facilitated.

Ach studied the influence of alcohol on perception. He caused a person to read through a small slit a continuous series of meaningless syllables written on a revolving drum, and showed that even one ounce of alcohol greatly reduced perception. Reis found that the mean error of the eye in the measurement of distance was increased after alcohol. Much of this older work is, however, unreliable, having been conducted by faulty methods ; Rivers sums up the situation by stating that alcohol in 20 c.c. doses is without any decided influence on mental fatigue. Whether depression of higher centres can account for the stimulation of the lower centres, or whether there is a direct stimulation of these centres as suggested by Binz, we have no means of absolutely determining at present. But it is not valid to assume that it must be a depressant action, since we know that alcohol produces an increase in the excitability in isolated frogs' nerves ; it stimulates ciliary movements and also accelerates the flow of plasma in certain plants.

Finally, alcohol and allied drugs give rise to a condition bearing a strong resemblance to the dissolution of insanity. Just as evolution is the building up from the most simple to the most complex, so dissolution is the breaking down from the most complex to the most simple, and in the insane the symptoms, hallucinations, &c., are the outcome of activity of nervous elements left uncontrolled by higher centres. So with both alcohol and insanity the latest developed centres are the first to go. Both the insane and the inebriated become more emotional and more easily excited; later they lose their voluntary control, and finally develop stupor. This process illustrates the law of dissolution.

Circulatory System.—That alcohol is a circulatory stimulant is popularly supposed to require no proof, but so much controversy has been occasioned that we describe the effect in some detail.

For this purpose the action will be considered under four headings: (1) pulse-rate, (2) heart, (3) peripheral vessels, (4) blood-pressure.

The *pulse-rate* is influenced by three factors which should be eliminated before we have a right to assert that alcohol by a direct action alters the rate of the heart. First, excitement in any form quickens the heart-beat, and as large doses of alcohol are apt to induce

excitement the experiments must be undertaken under conditions in which the patient can be kept free from all disturbing influences. Secondly, any form of peripheral irritation quickens the heart, and gastric irritation, which can be induced by strong alcohol, has the same effect. This error is avoided by seeing that the alcohol is well diluted. Thirdly, cardiac acceleration may be induced by any substance which lowers the blood-pressure. We shall see presently that this last suggestion is not applicable, at least, as far as moderate doses of alcohol are concerned, for the blood-pressure does not fall.

When alcohol is administered in small doses to those not addicted to the drug, and with due regard to the precautions mentioned, some slight acceleration ensues. If very big doses of alcohol obtain sudden access to the circulation the heart becomes decidedly slower. This effect is due to an action on the medulla, for it cannot be obtained if the vagi are first severed.

On the *heart* alcohol has a small but definite stimulant action. This is best shown on the isolated heart perfused through the coronary vessels by the method of Langendorff. The addition of a minute amount of alcohol (0.01 to 0.1 per cent.) to the circulating fluid causes a greater force of contraction, which is quite evident, though in no way comparable with that produced by the cardiac tonics. The same effect can be demonstrated on the pithed animal by measuring the outflow of blood from the heart before and after the administration of alcohol. This is done by recording the change in the volume of the heart with a cardiometer; for a successful experiment no other substance, such as chloroform, should have been previously administered.

The *vessels* of the body are not much affected by alcohol. It is true the superficial vessels are dilated considerably, and the warm glow and flushed face after taking alcohol are the result of this effect. But the superficial vessels do not behave quite in the same way as the internal vessels; atropine dilates the former and constricts the latter, and yet both effects are due to some central action. Alcohol at first tends to constrict the ordinary systemic vessels. This action is partially central, for we know that the medulla, directly or indirectly, is excited; but it is also peripheral, because perfusion either through the limb or intestinal vessels with a fluid containing alcohol always constricts the vessels at first. Large doses of alcohol dilate all the vessels throughout the body.

The *blood-pressure* generally rises; one reason so many people have asserted the contrary is because their experiments were vitiated by the use of an anæsthetic. A typical effect on blood-pressure is shown in Fig. 1; the animal in this case had had its cerebral hemispheres destroyed but had received no anæsthetic. The increased pressure is due to vaso-constriction, both central and peripheral in origin, and to the increased cardiac output.

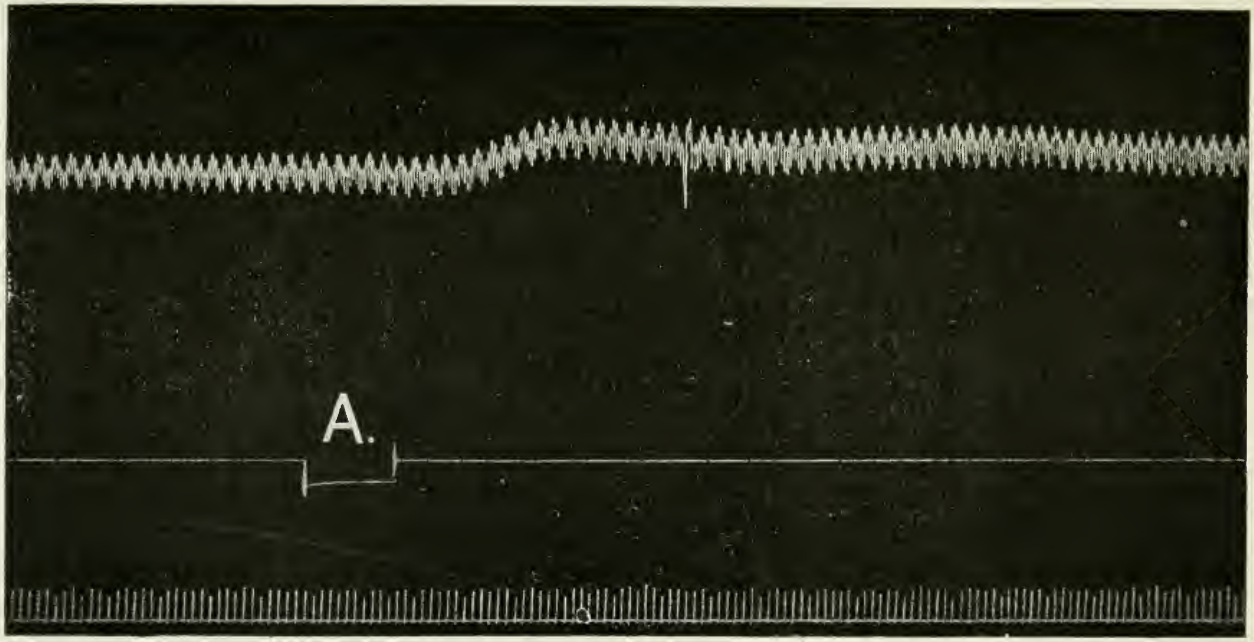


FIG. 1.—DOG (PITHED). BLOOD-PRESSURE.

Shows the effect of injecting at A 30 m. of diluted alcohol into one femoral vein. Note the rise in pressure and the enlarged volume-pulse. The rate of the heart is not much changed. This effect is mainly cardiac. Time = secs.
(All tracings should be read from left to right.)

Alcohol, then, has some title to the term circulatory stimulant. It probably produces its action on the heart by providing it with an easily assimilable source of energy, since alcohol perfused through an active isolated heart is used up and oxidised.

Temperature.—Alcohol lowers the body temperature, moderate doses from 1 to 3 oz. causing a fall of about half a degree Centigrade. This must be produced in one of two ways, either by increasing the heat loss or diminishing heat formation. The formation of heat remains almost unchanged with small doses ; an exaggerated elimination is the principal factor here concerned, the dilatation of the skin vessels allowing an excessive loss of heat. It is wrong, therefore, to take alcohol before going out into the cold. If taken at all it should be in a warm room after exposure to cold so that the vascular glow may not be the means of inducing a fall in temperature.

The evil effects of alcohol before exposure to a lower temperature have been demonstrated on animals. A number of small mammalia, some of which had received a dose of alcohol, were exposed to severe cold, and it was found that the animals which had received alcohol invariably succumbed first.

Action on Voluntary Muscle.—If a small injection of alcohol * is made into the lymph sac of a frog, a considerably increased amount of work can be obtained from the isolated nerve-muscle preparation, as compared with the work from the same muscle in the opposite leg, which has been kept free from the drug.

In man many experiments have been made with the ergograph ; these on the whole go to show that alcohol increases the capacity for work, either under certain conditions or in certain persons or for a certain time. Some, as Féré and Kraepelin, believe the increase is temporary only ; others, as Joteyko, that it only occurs in some people. Schnyder has shown that during starvation alcohol increases the working power of muscle, but to a less degree than other foodstuffs of equal energy-value. The work of Hellsten, who also used the ergograph, is the only investigation which proves the injurious influence of alcohol on the capacity for muscular work ; and he used the enormous dose of 80 grms. to obtain a decisive result.

Rivers has pointed out that in a properly devised experiment the work of the operator, who is living under definite rules, must be measured by the ergograph daily for some weeks. It is not valid to administer on one day a drug and regard any result on the work done on that day as due to the direct action of the drug ; the psychical effect of taking a drug will in itself influence the work. In his experiments, which are the most reliable on the ergograph, a potion was administered every day, sometimes containing alcohol and sometimes not, but the taste being masked. With such

* 0.01 grm. alcohol per gram of frog.

precautions Rivers found that alcohol in doses of 20 c.c. had no decided influence on muscular action.

Nevertheless it has been shown on dogs that alcohol, when present in low concentrations in the body, undergoes combustion at a more rapid rate during exercise than rest, and therefore supplies a greater amount of energy to the body.

Respiration.—Binz claims that alcohol has a direct effect on the respiratory centre. He says that alcoholic beverages have a decided though slight stimulating action, and that the effect is particularly striking with wines of rich bouquet and with brandy.

A large mass of evidence makes it quite clear that small doses of alcohol increase the oxygen absorption by about 3.5 per cent., and increase the carbonic acid by about 4.5 per cent. But whether this action depends on direct medullary excitation is another question. Jaquet, for example, whilst agreeing with the results of Binz, says they are due to gastric irritation. He claims to have obtained a similar effect by the administration of an aqueous extract of mustard, and states that the administration of morphine in small doses obliterates the effect of both alcohol and mustard by depressing the excitability of the mucous membrane. It cannot be accepted, however, that alcohol produces an effect on the stomach in any way comparable, as regards local irritation, with that of mustard ; and the use of morphine is not legitimate in this experiment since it has a decided depressant effect on respiration, and no action on sensory nerve-endings.

The most probable explanation of the stimulant action of alcohol on respiration is that it is due to an indirect effect. Alcohol causes an increased loss of heat from the surface of the body, and, therefore, heat production is augmented to make good the loss—the fall of temperature, which is very small, being the difference between these two processes. This means that there is a compensatory increase in the oxygen intake and increased combustion. According to this explanation alcohol should be regarded as an indirect stimulant to respiration.

Metabolism.—Alcohol in moderate doses is oxidised almost entirely in the body, and therefore must yield energy. Atwater and Benedict showed that when 2½ oz. were given daily to a man, never more than 2 per cent. was excreted unchanged in the urine. Since no intermediate products of oxidation have been found, it is generally assumed that this alcohol is completely oxidised to carbonic acid and water. Oxidation is accomplished slowly because the amount of alcohol found circulating in the blood soon after its administration by the stomach is roughly proportional to the amount given, and, especially after small doses, remains almost constant for at least two hours.

Alcohol a Fat Sparer.—The most reliable experiments on alcohol are those of Atwater and Benedict. They required a man to

enter a large and sufficiently ventilated chamber, in which he lived for several days, and which served both as a calorimeter and a respiratory chamber. By this means both the total heat given out and the interchange through the lungs could be measured. Work was performed when necessary by turning a fixed bicycle wheel which revolved a dynamo: the current from this was sent through a lamp and the heat given out recorded the work done. The diet and excreta were daily analysed. By experiments in this fashion it was shown that if 2½ oz. of alcohol be made to replace fat of an equivalent calorific value from a fixed diet, the same amount of energy is utilised still, and roughly the same heat is given off. Now we know that alcohol is oxidised, and since no extra heat is given out it must be usefully burned, *i.e.* it spares the oxidation of fat. When the amount of alcohol administered is small, it even does this isodynamically. This property may account for the stoutness of the beer-drinker.

Can Alcohol Spare Protein?—Supposing a man to be placed in a condition of nitrogenous equilibrium with food of an energy-value just sufficient to supply the needs of the body—*i.e.* there is neither loss nor gain in weight—it is found that when carbohydrate is suddenly withdrawn an increased loss of nitrogen is immediately produced. This means that the tissue-protein is oxidised for the needs of the body. The loss may be avoided by substituting an equivalent amount of fat for the carbohydrate, but if alcohol is substituted the increased loss of nitrogen sometimes remains. Indeed, we can go even further than this, and show that if a man, taking a fixed diet, is in nitrogenous equilibrium, the simple addition of alcohol to his diet may increase nitrogenous loss. Besides supplying the body with some energy, alcohol, therefore, exerts a toxic effect, in some people resulting in an increased protein metabolism.

Supposing now that experiments of this type, instead of occupying only a few days, are continued over a longer period. The food value of the diet remains unchanged, but the tissues apparently become tolerant to the poisonous action of the alcohol. It no longer produces a toxic effect, and so can act now as a protein sparer. In the majority of people, however, alcohol would seem to act as a protein sparer throughout.

Rosemann in a series of experiments added alcohol to a dietary just capable of maintaining nitrogenous equilibrium. The alcohol was administered for eighteen days, and the amount was increased from 20 c.c. on the first day to 100 c.c. per diem towards the end of the time. He showed that from the twelfth to the eighteenth day there was an average gain of 2 grams of nitrogen to the body, *i.e.* in the week the body gained in weight about a pound, solely from the added alcohol.

Experiments of this type show that if fats and carbohydrates are removed from an efficient dietary and replaced by alcohol there is first an increased loss of nitrogen (toxic action); but in a

few days the tissues adapt themselves to the changed conditions and the metabolism again assumes a condition of equilibrium at about the same level as before. Yet if carbohydrate is removed without replacement by alcohol the diet is insufficient and is shown by a considerable loss of nitrogen.

One experiment by Offer on a healthy man who was not accustomed to taking alcohol will make the situation clear. The following figures show the daily gain or loss of nitrogen to the body under the conditions mentioned :—

	Grm.	
Period 1.—Diet alone.	Loss, 0.3441.	Body nearly in nitrogenous equilibrium.
Period 2.—Diet + 100 grams of alcohol.	Loss, 1.1689.	Toxic action on tissues.
Period 3.—Diet + 100 grams of alcohol.	Gain, 0.2335.	Tolerance beginning to be established, and alcohol acting as a protein-sparing foodstuff.
Period 4.—Diet alone.	Loss, 0.0110.	
Period 5.—Diet with added fat.	Gain, 1.5654.	

The increased nitrogenous breakdown seen in the second period in this experiment is apparently due to the effect of alcohol on the tissue-cells. The equilibrium which develops in the later stages is the effect of tolerance, the cells now being able to oxidise the alcohol as it reaches them. Other and probably more reliable experiments than these have failed to show this toxic action on the tissues, and it is now generally accepted that alcohol can spare protein in the same way and to the same extent as carbohydrates such as starch and sugar.

Now that we understand how alcohol affects the tissues we will consider the question "*Is alcohol a food?*" It has been already pointed out that it is a fat-sparer and also a protein-sparer, especially in those moderately addicted to its use. Further, it surpasses starch and sugar in alimentary value because weight for weight in contains more energy. This evidence alone would unquestionably place it in the category of foods. In excessive amounts it has, however, a toxic action. That is to say, so long as the amount of alcohol in the body can be oxidised and destroyed by the tissues it acts as a food. If, however, this amount is exceeded, the alcohol exerts its specific action on the central nervous system and induces certain toxic effects ; and in this sense it is a drug. In this connexion it is well to remember that an excess of almost any food substance in the blood may induce toxic effects : sugar, for example, may in time cause fatty degeneration of the tissues. About 0.1 per cent. of alcohol in the blood is an amount with which the tissues can readily deal, and is unlikely to cause much action

apart from its effect on metabolism. Alcohol to the extent of 0.5 per cent. in the blood is sufficient to cause profound intoxication. The food value of alcohol depends on the dose and the degree of tolerance. It is a food in so far as it is oxidised in the body: it is a poison to the tissues when an amount is present in the system greater than can be dealt with at the time. Its special value as a food in disease is determined by its very rapid absorption under circumstances when ordinary foods are only absorbed with great difficulty.

Finally, it has been shown that alcohol is a normal constituent of mammalian tissues; thus 0.0017 per cent. of alcohol is present in rabbits' livers, muscles, and brain. Controversy, however, still exists as to the origin of this alcohol. Some assert that it is derived from normal putrefaction by yeasts and other organisms in the alimentary canal; others believe that it is an intermediate product in the oxidation of glucose. The second view is probably correct, since alcohol can be distilled from the tissues of decerebrate animals many hours after the removal of the alimentary canal. But whatever the explanation may be, the fact remains that alcohol is a normal constituent of mammalian tissues.

Excretion.—Alcohol in moderate doses undergoes oxidation in the body, but 1 or 2 per cent. is excreted in the urine. The kidneys have no special excretory power, and the urine has been found to contain no more alcohol than the exact proportion contained in the blood.

Methyl Alcohol, or wood spirit, has the appearance, odour, and taste of common alcohol. It produces, at first, effects like those of common alcohol, except that during the intoxication the excitement is greater and the muscular weakness is more pronounced.

Methyl alcohol is oxidised in the body considerably slower than ethyl alcohol, so that the intoxicating effects of a single dose last longer. Moreover, the oxidation is incomplete, formic acid and perhaps formic aldehyde being formed. These poisons give rise to optic neuritis and subsequently to optic atrophy. Wood spirit has been substituted for ethyl alcohol as an intoxicant, especially in America, and it has been estimated that from 60 to 75 per cent. of those who have taken 4 oz. of this alcohol have died during the intoxication, or have become permanently blind on recovery.

MATERIA MEDICA

1. **Alcohol Absolutum.**—Should contain **at least 99 per cent. alcohol,** $C_2H_5.OH$.
2. **Spiritus Rectificatus.**—Rectified spirit. **Ethyl Hydroxide (90 per cent. by volume).**
3. **Vinum Xericum.**—Sherry.
   Contains not less than **16 per cent. by volume of alcohol.**
4. **Vinum Aurantii.**—Orange Wine.
   Contains from **10 to 12 per cent. alcohol.**

CHAPTER IV

ANÆSTHETICS. NARCOTICS. HYPNOTICS

The term narcotic or soporific in its widest sense is applied to a drug which produces cerebral depression. The narcotics may be divided into two classes: the specific, which act by their direct chemical affinity for nerve-cells, such as the bromides or morphine; and the indifferent, which probably act physically. Only the latter group are considered in this chapter, and they may be subdivided into *anæsthetics*, drugs producing unconsciousness; *hypnotics*, for promoting sleep; and *narcotics* proper, substances which give rise to a condition resembling coma. It must not be imagined that there is any hard-and-fast line between these artificial subdivisions; on the contrary, all the members have the same type of action, but owing to individual differences in absorption and excretion some are specially adapted for particular uses. Hypnotics, although inducing the same general effects as the anæsthetics, are used only to produce imperfect consciousness—sleep; because, being comparatively slowly absorbed and excreted, a definite quantity of the substance will remain in the blood for some hours, and so prolong the depressant action. Narcotics or hypnotics administered in large doses give rise to complete anæsthesia. Urethane, for example, when given to a rabbit in doses of 1 or 2 grs. behaves as a mild hypnotic, but if an injection of 100 grs. is made, it forms an excellent and complete anæsthetic. Such an anæsthetic would not be suitable for man on account of the prolonged action of the drug—about twenty-four hours—and on account of the difficulty of just gauging the dose, so that whilst anæsthesia is complete the medulla retains its activity. The term anæsthetic has come to be used in a limited sense for drugs which are very rapidly absorbed and excreted, *i.e.* the volatile drugs chloroform, ether, &c. With such the effect lasts only so long as the administration is continued. They are quite unsuitable as hypnotics because they act for too short a time.

CHLOROFORM

From the most remote periods surgeons have sought the means to relieve the pain of operations. The internal administration of drugs seems to have been the time-honoured method. In China Indian hemp was used for this purpose. The stupor produced

by compressing the carotids was employed by the Assyrians, and hypnotism was practised in the East. In later times advantage was taken of the intoxication produced by alcohol.

The first suggestion to produce anæsthesia by the inhalation of drugs was made by Davy in 1800, when he discovered by experiment on himself that nitrous oxide had the power of relieving toothache; the properties of this body were not properly realised, however, till some fifty years later. Morton first made use of ether as an anæsthetic in 1846, and Simpson is credited, though wrongly, with having discovered the use of chloroform about a year later.

Chloroform is a colourless volatile liquid. It sinks in water, in which it is soluble to about $\frac{1}{2}$ per cent., but it is freely soluble in alcohol, ether, olive oil, and turpentine. Sometimes, especially as a result of exposure to light, decomposition occurs and carbonyl chloride, free chlorine or hydrochloric acid—all of which are irritant—may be formed thus:—

$$4CHCl_3 + 3O_2 = 4COCl_2 + 2H_2O + 2Cl_2$$
$$COCl_2 + H_2O = CO_2 + 2HCl.$$

Deaths during anæsthesia are due to the anæsthetic and not to the trace of impurity which may be present in it. Chloroform has much the same action when applied externally as alcohol, but is more irritant. If it is dropped on the skin it gives rise to the feeling of burning followed by blunting of sensation. If the vapour is not allowed to evaporate, or if the chloroform is rubbed into the skin, it acts as a rubefacient and irritant, and should it contain alkaloids in solution their absorption is facilitated.

Symptoms of Inhalation and Action on the Central Nervous System.—The symptoms of chloroform inhalation closely resemble those of alcohol-narcosis. With chloroform the excitement stage is very much shorter owing to the rapid absorption from the large area of the lung-capillaries, thereby inducing the rapid onset of anæsthesia. For convenience of description the symptoms are divided into three stages. (1) A *preliminary stage* characterised by a feeling of excitement and by various reflex effects. The local action of the anæsthetic on the respiratory passages gives rise to smarting in the nose and conjunctiva, and reflexly to coughing and salivation with hypersecretion from all mucous membranes with which the anæsthetic comes in contact. The action of the vapour on the nasal mucous membrane induces two other reflex effects. The first is on respiration; not uncommonly the animal holds its breath voluntarily until forced to breathe by asphyxia. If a little chloroform is held near a rabbit's nose, the animal stops breathing before any of the vapour has had time to be absorbed. This is due to irritation of the nerve-endings of the fifth, for the effect is not seen if either the fifth nerves have been cut, or if the interior of the nose has been painted with cocaine—a drug which paralyses sensory nerve-fibrils — before the anæsthetic is

administered. The second reflex is on the heart, which is slowed. This also is produced by irritation of the fifth nerve-endings in the nose, and does not occur if the nasal mucous membrane has been painted with some local anæsthetic. During this stage the face is somewhat flushed, and the excitement induces a quickened pulse and dilated pupils.

(2) The *second stage* is characterised by great excitement. The patient loses self-control, struggles violently, and exhibits all the uproariousness of the drunkard; and here, as in the case of alcohol, his language and behaviour are largely controlled by his habitual mode of thought. There is a general feeling of stiffness, and sensation is blunted. The respiration is irregular from the struggling; the pulse is accelerated and the pupil dilated, both as a result of the excitement.

(3) The *third or anæsthetic stage* now gradually ensues. The muscular system slowly relaxes, and the reflexes disappear, the pupillary reflex being one of the last to go. The pulse and respiration are both somewhat slower than normal, and the pupil is a little contracted, being in much the same condition as it is during ordinary sleep.

The symptoms of the various stages may be seen from the following table:—

Stage 1.	Irritant action of the vapour on the nasal and bronchial mucous membrane.
	Reflex effects—coughing, salivation, respiratory cardiac.
	Disturbances of judgment.
Disorganised consciousness and analgesia.	Loss of memory and self-control.
	Emotional tendencies.
	Disturbances of special senses.
	Analgesia.
	Vertigo and ataxia.
	Quickened pulse and rise in blood-pressure.
	Increased respiration.
	Dilated pupils.
Stage 2.	Coughing, retching, vomiting.
	Delirium varying from shouting to inarticulate muttering.
Excitement and unconsciousness.	Tonic and clonic muscular spasm.
	Reflexes diminished but still present.
	Unconsciousness.
	Respiration irregular from the struggling.
	Pulse accelerated and pupil dilated, both from excitement.
Stage 3.	Muscular relaxation.
	Loss of reflexes.
Surgical anæsthesia.	Breathing regular, often "snoring."
	Decrease of respiratory exchange.
	Fall of temperature.
	Fall of blood-pressure.
	Pupil small, but does not react to light.

Stage 4.	Loss of bladder and rectal reflexes.
Leading to bulbar paralysis.	Paralysis of vaso-motor centre (great fall of blood-pressure).
	Paralysis of respiratory centre.
	Widely dilated pupils.
	Great depression of cardiac muscle.

The action of anæsthetics is characterised by the same progressive paralysis of the central nervous system that has been described with alcohol, except that, on account of the rapid onset, the excitement is even wilder. As in the case of alcohol, so here, some authorities regard the excitement as evidence of stimulation; and the same arguments are applicable here as those which have been already discussed for alcohol, but with the additional evidence that excitation of the cortical motor areas gives rise to a diminished effect after chloroform inhalation.

All narcotic drugs of this class (fatty series) probably affect the sensory part of the central nervous system before the motor. This has been shown for chloroform on the spinal cord of animals by destroying a limited small portion of the pia mater. Inhalation of chloroform will not affect this portion of the cord since the blood-vessels are destroyed. Supposing Fig. 2 to represent the spinal cord, and B to be the portion deprived of its pia mater, stimulation of the sensory nerves N_1 produces no reflexes. But stimulation of the sensory nerve N_2 gives rise to reflexes not only in the part B but in the rest of the cord A, *i.e.* the motor cells in the portion A must still be intact.

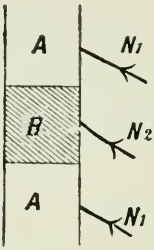


FIG. 2.—DIAGRAMMATIC VIEW OF THE SPINAL CORD, OF WHICH THE PORTION B HAS BEEN DEPRIVED OF ITS PIA MATER. (CAT OR DOG.)

During anæsthesia excitation of the afferent nerves N_1 produces no reflexes, but excitation of N_2 produces reflexes not only in parts of the body supplied from B but also in those parts supplied by A. Hence the anæsthetic does not affect the motor cells in A.

Later, the motor part of the cord is paralysed also, since direct electrical stimulation produces no effect. The medulla is paralysed last of all.

Action on Respiration.—The effect of chloroform narcosis on respiration is much the same as that of any other form of narcosis. In the first stage the irritant effect of the vapour on the nasal mucous membrane gives rise to either slowing or cessation of the respiratory movements. These effects are reflex, and are produced by irritation of the fifth nerve-endings. During the excitement stage respiration is necessarily irregular, and as a result of the struggling it often happens that a large amount of the vapour is innaled. In the anæsthetic period the respiration is slower and shallower than normal. The Hyderabad Commission concluded from their experiments that interference with or paralysis of respira-

tion was the only means by which the heart's safety was jeopardised. We now know that this Commission was wrong in its finding, and that uncomplicated respiratory failure never causes death if artificial respiration is resorted to. Failure of respiration is generally due to great fall of blood-pressure, and its restoration is dependent on the recovery of the blood-pressure (Fig. 3). The failure of respiration during the early period of anæsthesia happens as frequently after as it does before the heart stops, and, in any case, is of little significance compared to the condition of the heart.

The respiratory exchange undergoes considerable diminution during chloroform narcosis, sometimes 50 or 60 per cent., mainly as a result of immobility and fall of temperature. The exchange remains small for two or three hours after recovery from anæsthesia.

Circulation.—Death from chloroform usually occurs in one of two ways: (1) It may be due to an overdose, though this does not occur with experienced administrators: the general effects of overdose are considered later. (2) It may occur in the early stages when narcosis is light and overdose may be excluded. Sudden death during light chloroform anæsthesia in animals can be produced in two different ways. Death can be induced readily in dogs by the inhalation of a few whi.'s of concentrated chloroform vapour. This effect is due to sudden inhibition of the heart, brought about by the rapid absorption of a concentrated dose of chloroform from the great surface of pulmonary capillaries. The inhibition is the direct result of excitement of the vagal centre in the medulla, because death does not occur in dogs if the vagi have been first severed, or if a dose of atropine—an alkaloid which paralyses the vagal endings—has been administered previously. Further, when such an inhibition of the heart has been induced, section of the two vagi, by cutting off the medullary effect, will release the heart; the beat will once again recover its normal character, and the blood-pressure will bound up (Fig. 3).

The sudden administration of anything over 2 per cent. in the air may lead to dangerous or persistent inhibition. At no period should more than 0.5 per cent. be given, and 0.2 per cent. or less is sufficient to keep an anæsthetised man or dog unconscious, and this may lead during complete anæsthesia to 0.05 per cent. of chloroform in the venous blood, though the central nervous system will contain a higher percentage than this.

We believe then that central vagal inhibition may be a factor in the causation of sudden death from chloroform. To avoid such an effect, it has been suggested that all patients should receive a dose of atropine before they are anæsthetised, thereby, to some extent, blocking the central impulses. But the most important fact to bear in mind is that the anæsthetic must be administered very slowly in the early stages. The centre then loses its irritability to chloroform vapour and soon undergoes depression. Inhibition when once induced in man is very difficult to treat. The

patient at one time is apparently breathing well and has a good pulse and contracted pupils. In a moment his pulse flickers and stops, and his respiration ceases generally some ten to thirty seconds later: the pupils are still contracted, showing that the effect is not the result of a very large amount of chloroform such as might be the cause of death during the fourth stage of anæsthesia. Under these circumstances artificial respiration must be performed, and measures adopted to bring back the heart-beat. The best hope of success is from the injection of a solution of atropine into a vein. It should be washed well in with a saline solution so that it may reach the heart, depress the vagal terminations, and so overcome the inhibition. This treatment is likely to be successful if the heart has not been completely inhibited, as in Fig. 3.

Almost any drug which depresses cardiac muscle, like chloroform or potash salts, may occasionally cause the ventricle to fibrillate (*see under* Digitalis). This tendency is especially marked in cats under light chloroform anæsthesia. This fibrillation, or non-co-ordinated contraction of the ventricular muscle, is another cause of sudden death during the early stages of anæsthesia. It may be prevented by maintaining a full degree of anæsthesia. The condition once produced is uninfluenced by section of the vagi or the administration of atropine.

During light anæsthesia in cats powerful stimulation of the sympathetic nerves may cause the ventricles abruptly to fibrillate, and as cats have a very active sympathetic system it has been suggested that whilst the chloroform is the predisposing cause of sudden death sympathetic stimulation in one form or another (subconscious emotional state of struggling or perhaps the liberation of adrenaline) may be the exciting cause (Fig. 4).

Therefore, during light anæsthesia death in the dog, an animal with much vagotonia, occurs from vagal inhibition, and in the cat, which possesses considerable sympatheticotonia, from fibrillation of the ventricles. In both animals the death is associated with sudden alterations in the amount of drug inhaled. In man there is reason to think that death may occur from either of these causes. Sudden mental shock causes the heart-beat of some people to quicken and others to slow, according to whether they belong to the vagal or sympathetic type, and we believe that death may occur during light anæsthesia by one or other of the methods described for the dog and cat respectively.

The inhalation of chloroform vapour, besides the vagal centre, also at first stimulates the vaso-motor centre in the medulla. This can be shown by the cross-circulation experiments of Gaskell and Shore. Two rabbits, A and B, are connected together so that the cardiac end of one carotid artery of A is joined to the cranial end of one carotid of B; also the cranial end of one jugular vein of B was similarly joined to the cardiac end of one jugular of A. If chloroform is inhaled by rabbit A it is absorbed by the lungs and

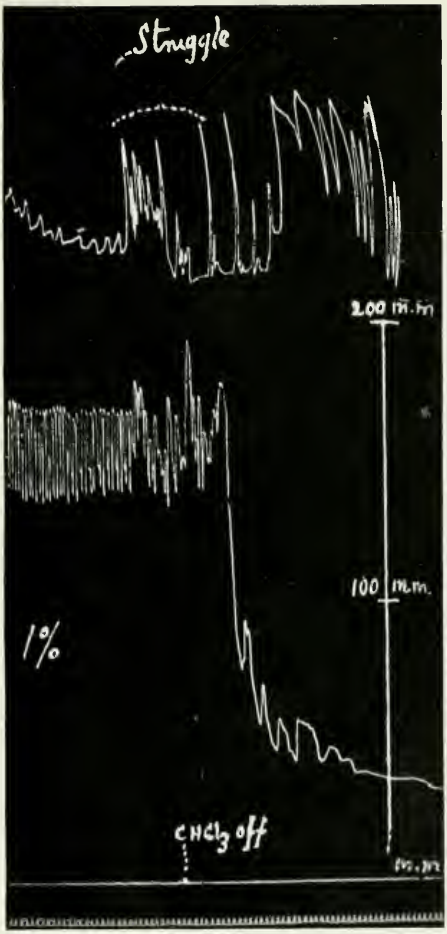


FIG. 2A.—CAT. RESPIRATION AND B.P.

Ventricular fibrillation caused by struggling during the induction period. Anæsthesia induced by 1.5 per cent. chloroform, then 2 per cent., then reversion to 1 per cent. when the animal began to struggle. The heart became very irregular, the chloroform was entirely removed, and the ventricles fibrillated a few seconds later. Time = secs. (Levy.)

To face p. 36.

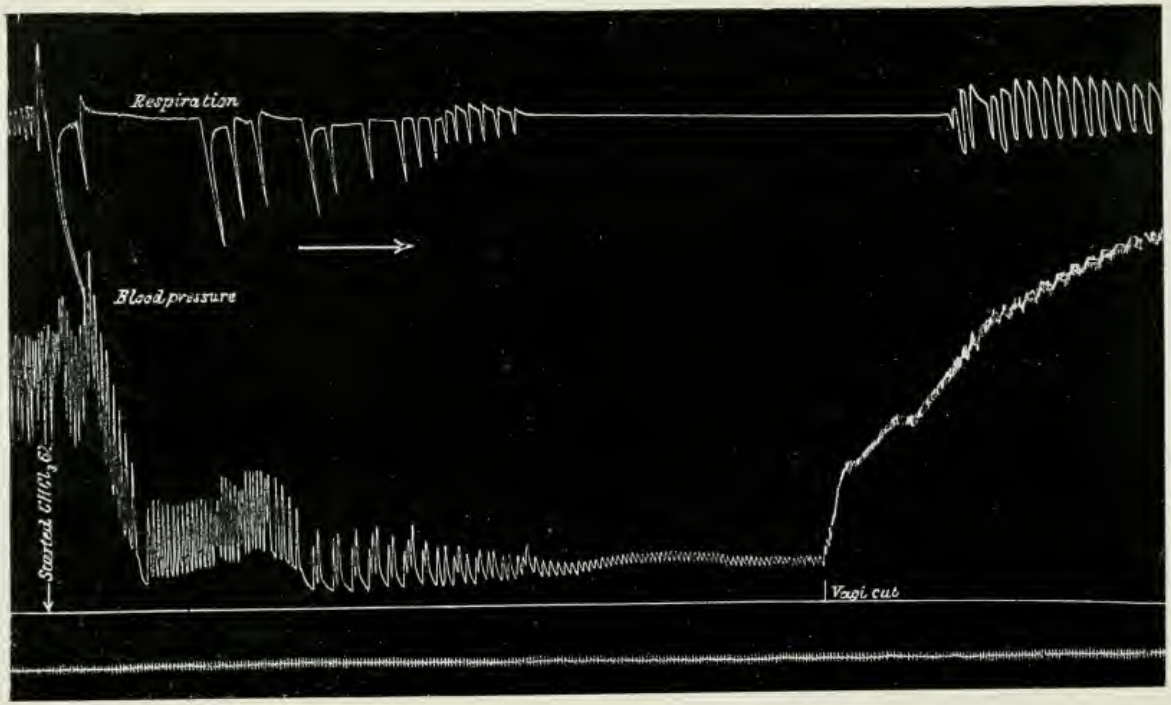


FIG. 3.—DOG WHICH HAS HAD NO VOLATILE ANÆSTHETIC.

The cardiac inhibition after concentrated $CHCl_3$ is clearly shown. The cessation of respiration is due to the deficient blood-supply to the centre. Section of the vagi releases the heart, and with the circulatory recovery respiration begins again. (Embley.)

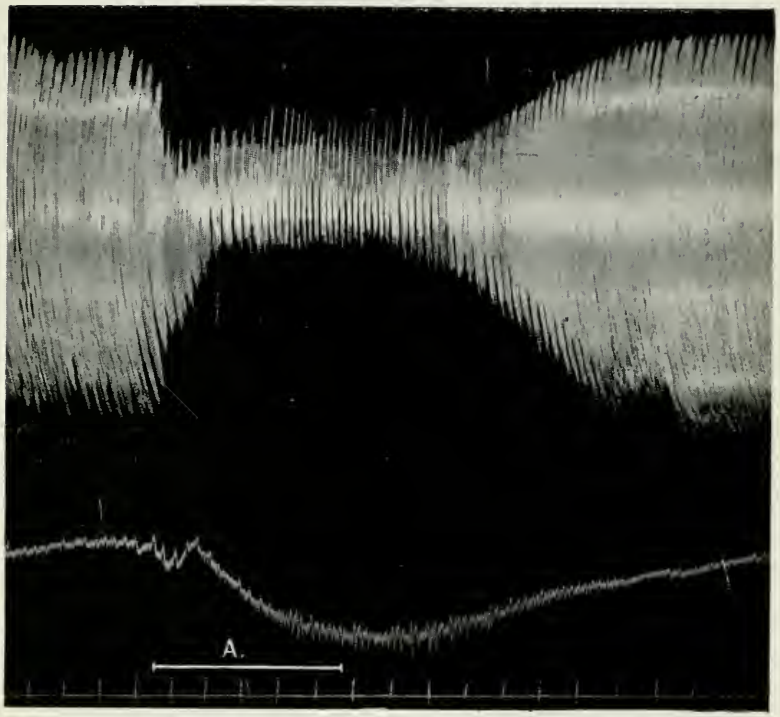


FIG. 4.—DOG (DECEREBRATE). LEFT VENTRICLE AND BLOOD-PRESSURE.

Upper curve represents the extent of the movements of the left ventricle as measured by the pull on a weighted lever. Upstroke = systole. Lower curve represents blood-pressure. During the period A chloroform was inhaled (about 2 to 3 per cent.). Note the immediate weakening of the cardiac contractions and the slower recovery. The fall of blood-pressure is due to this effect. Time = 10 secs.

To face p. 57.

passes immediately to the left heart. The cardiac muscle is depressed, and so the output is diminished and the blood-pressure falls. Some of this blood then passes by the cross-circulation directly to the brain of B, where it stimulates the medulla (vasomotor centre); the peripheral vessels in consequence constrict, and the blood-pressure rises.

Chloroform directly depresses all forms of muscular tissue throughout the body. The excised heart of an animal beats regularly and rhythmically so long as the coronary arteries are perfused with warm Ringer's solution or defibrinated blood, and the movements can easily be recorded by a lever. Chloroform markedly diminishes the force of contraction of the muscle: the effect quickly passes off when the anæsthetic is removed. Fig. 4 shows the action on an intact heart; the blood-pressure falls during the chloroform inhalation "A" just in proportion as the force of contraction of the ventricle (upper curve) becomes less.

As the contractile power of the heart-muscle diminishes the organ dilates; the walls are no longer capable of efficiently contracting on the blood they contain and the heart becomes more and more gorged with blood. This can be shown by measuring the volume of the heart by means of the cardiometer. Fig. 5 demonstrates the effect of chloroform under such conditions; the tracing shows both a rapid dilatation of the heart and marked diminution of the output. The drug acts on the muscle directly, and in this respect is comparable with the potassium ion.

Chloroform depresses the plain muscle of the vessels. Oncometer experiments show that the net result of chloroform inhalation on the vessels of the intestines, spleen, and kidney is dilatation. The skin-vessels dilate early, and one of the first effects of inhalation is flushing of the face. It is not due to the direct action of the chloroform, but to excitation of the medulla, which, during the stage of excitement, both constricts internal vessels, and, therefore, raises blood-pressure, and dilates the skin-vessels. This transient constriction soon gives place to dilatation, for the ultimate action both on the centre and periphery is paralytic. After a short rise, due to the central stimulation, the blood-pressure falls as the result of the diminished output from the heart and the vaso-dilatation.

Vaso-dilatation is well shown by the perfusion of any isolated organ. If, for example, the intestine is perfused through its artery with defibrinated blood and the outflow from the vein measured, the addition of a little chloroform to the circulating fluid, after initial constriction, increases the outflow from the vein. This effect might conceivably be caused by either depression of nerve-endings or muscle. That the effect is upon muscle is shown by perfusion of the lungs through the pulmonary artery. These vessels contain no nerve-supply, and yet they dilate under chloroform after the typical primary constriction.

Other Effects.—Moderate anæsthesia has but little effect on the movements of the bladder, intestines, or uterus; and during parturition the uterine contractions are very little influenced. Deep anæsthesia diminishes all movements of plain muscle.

The temperature steadily falls. With ordinary precautions this is not more than about half a degree in half an hour, although after prolonged anæsthesia drops of even 5° or 6° F. have been recorded. The cause must be looked for (1) in the vascular dilatation of the skin, thereby producing an increased output of heat,

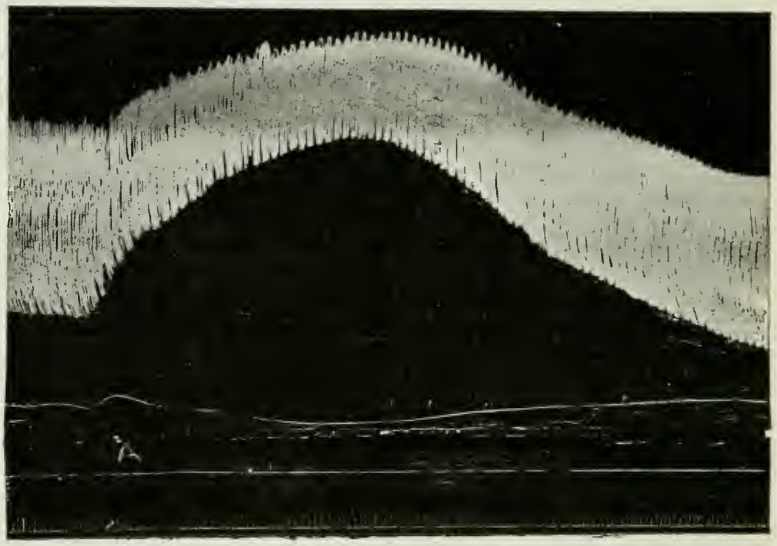


FIG. 5.—DOG (DECEREBRATE). CARDIOMETER (*i.e.* HEART-VOLUME) AND B.P.

During the period A 3 or 4 per cent. of $CHCl_3$ in air was inhaled Systole (downstroke) becomes progressively weaker, and cardiac tonus is diminished, so the heart becomes distended with blood, only a small proportion of which is expelled during systole. The fall in B.P. is due to this effect on the heart; as the cardiac systole improves the blood-pressure rises. Time = secs.

and (2) the absence of voluntary movements and the general depression of activity of the tissues, so diminishing the production of heat.

Chloroform increases the excretion of nitrogen, chlorides, phosphates, and sulphates in the urine. This autolysis of tissue is not due to greater oxidation, because the increase of nitrogen is in the form of amino-acids and purins, whilst the sulphur is in a complex and unoxidised form, such as cystin or related bodies. After prolonged chloroform inhalation, fatty degeneration in the liver, heart, and kidneys has been described. These cases of delayed chloroform poisoning begin any time from twelve hours to four days after a prolonged anæsthesia and are most common in children.

The symptoms generally begin with vomiting, a rapid pulse, and acetonuria; delirium follows and passes into rapidly fatal coma. Small amounts of chloroform administered for several months have been known to give rise to atrophic cirrhosis of the liver.

Chloroform or ether added to shed blood dissolves the red corpuscles and liberates the hæmoglobin ; possibly the jaundice which sometimes follows anæsthesia may be due to this cause.

Chloroform and ether are excreted mainly by the lungs. A small amount of chloroform seems to be oxidised in the tissues, for both the chlorides and acidity of the urine are increased, the latter owing to the hydrochloric acid formed by the combustion. Chloroform is one of the many drugs which produce glycuronic acid in the urine ; this is a substance which reduces Fehling's solution, and sometimes gives rise to the idea that sugar is present. Yeast will not grow in such a urine.

ETHER

The action of ether so closely resembles that of chloroform that it will be necessary only to mention the differences in action between the two drugs.

Common ether is a colourless neutral volatile and inflammable liquid miscible in alcohol and fatty oils. It is prepared from alcohol by heating the latter with sulphuric acid at a temperature of 140° C., when the following reaction occurs :—

$$C_2H_5OH + H_2SO_4 = H_2O + C_2H_5HSO_4$$
$$C_2H_5HSO_4 + C_2H_5OH = H_2SO_4 + \begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\Big\} O$$

It is used to dissolve fats and waxes, such as plugs of cerumen from the external auditory meatus. The presence of water or alcohol may be detected in ether by adding to it a little oil of copaiva, which forms an emulsion if either of these two impurities is present.

Ether is used for three entirely different purposes :—(1) As a local anæsthetic ; (2) internally for its action on the stomach and circulation ; and (3) as a general anæsthetic.

When it is used as a local anæsthetic a fine spray of ether is projected on to the part to be anæsthetised, and this renders the skin or mucous membrane hard and white. The method answers well for small and superficial operations, but damage or even sloughing of the tissues may follow prolonged freezing.

Chlorides of methyl and ethyl are superior to the ether spray as local anæsthetics.

Taken *internally* by the mouth, ether has a narcotic action somewhat similar to that of alcohol. It increases the secretion and movements of the stomach and expels flatus ; it is, therefore, used as a carminative. In medicinal doses ether has little direct

action on the heart, but it quickens the pulse reflexly from its irritant effect on the mouth and stomach. Its action is very similar to that of alcohol, only it is absorbed and excreted quicker: the symptoms develop, therefore, more rapidly, and the intoxication is shorter.

Ether, used as a general *anæsthetic*, is only about a quarter as toxic to the central nervous system as chloroform, and is about four times as safe. It must be administered much more concentrated and is, therefore, more disagreeable, and may give rise to considerable bronchial irritation. For this reason it is generally unsuitable as an anæsthetic for elderly people and children. Inhalation of ether produces surgical anæsthesia more slowly than chloroform, and the excitement stage is both more marked and

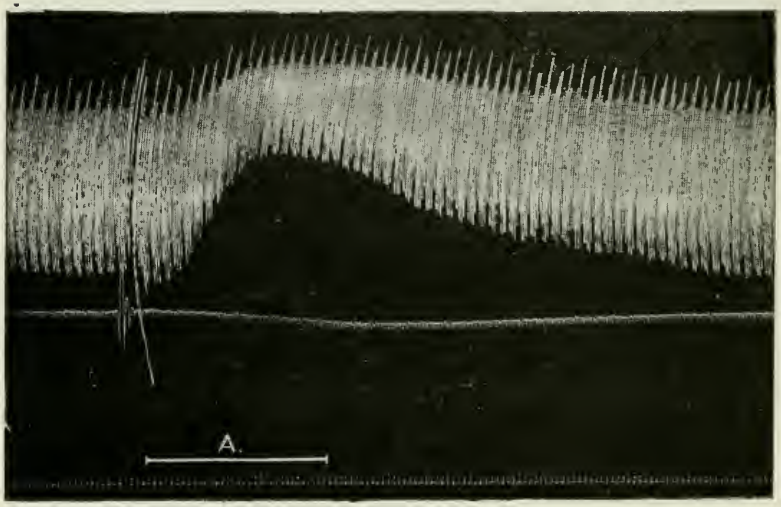


FIG. 6.—DOG (DECEREBRATE). CARDIOMETER AND BLOOD-PRESSURE.

At A an inhalation of nearly pure ether was given. The systolic contractions are considerably weakened, and the heart tends to become distended with blood; but the effect is much less serious than that induced by 2 or 3 per cent. $CHCl_3$, and this is also shown by the relatively smaller fall in blood-pressure. Time = secs. (Compare with Fig. 5.)

prolonged than with the latter drug. Between 4 and 5 per cent. ether by volume in the air may be required before complete anæsthesia is produced, and this gives rise to perhaps 0.13 per cent. in the blood.

The toxic effect of ether on muscle and nerve is much less than that of chloroform. Sudden death from central vagal stimulation is unknown. The force of cardiac contractions is but little affected even by very deep anæsthesia, and dilatation of the heart comparable to that seen during chloroform inhalation is never observed (*cf.* Figs. 5 and 6). Blood-pressure is little affected. But besides the closed method, ether may be given on a loose mask like

chloroform. In this open method the patient has no feeling of suffocation and little bronchial irritation, but twenty minutes or more are required to produce anæsthesia. A third method of inserting a cannula into a vein and slowly injecting a solution of ether has also been tried; in this the dose is known exactly, respiratory troubles are absent, and consciousness returns so soon as the injection ceases.

Acetic Ether ($CH_3.COOC_2H_5$) acts like ether, but is pleasanter to take. It is used as a mild antispasmodic and diaphoretic.

ETHYL BROMIDE

Ethyl bromide is a colourless liquid with a pleasant taste decomposed by exposure to air and sunlight. Its boiling-point is about 39°.

When inhaled it rapidly produces analgesia at a time when ordinary sensations are still appreciated, so that painless operations may be performed under its influence without complete loss of consciousness. If about 20 c.c. of the liquid are placed on a mask the patient is ready for short operations, incisions, and the like in about thirty seconds, but the anæsthesia only lasts a few minutes. It is useless for deep anæsthesia, as respiratory paralysis ensues before muscular tone is lost.

Ethyl bromide is partly broken down in the body: the garlic-like odour of the breath, which may last some days after an inhalation, shows that some bromine is retained. Some of it may be converted into the more toxic $C_2H_4Br_2$.

The corneal reflex is of little value for determining the patient's condition with this anæsthetic, since it is rarely lost: needle-pricks form a more reliable test. Several deaths have resulted from its use.

Ethylene dibromide is a liquid boiling at 131°. It is valueless as an anæsthetic, but is sometimes used as a sedative in epilepsy instead of the inorganic bromides. Caution is required in its administration, as besides acting like ethyl bromide on the respiratory centre it also weakens the heart.

ETHYL CHLORIDE

Ethyl chloride when slightly compressed is a colourless mobile liquid boiling at 12.5°. It is largely used to produce local anæsthesia,

the tubes in which it is stored being provided with a tap by means of which a fine jet of the liquid may be directed on the part to be anæsthetised. It may be inhaled to produce general anæsthesia, and then acts like ethyl bromide. A few c.c. placed on a mask produces anæsthesia in about two minutes and lasting ten minutes, but the reflexes are not lost, and muscular relaxation is not complete. Deaths have occurred from its use.

BROMOFORM

Bromoform $CHBr_3$ is a colourless heavy liquid boiling at 149°. Formerly, in spite of its feeble volatility, it was sometimes used to produce anæsthesia instead of chloroform. The anæsthesia is deeper and more prolonged than that of chloroform. It is now sometimes used in doses up to 2 m. to relieve the spasm of whooping cough.

NITROUS OXIDE, N_2O (not official)

This colourless non-odorous gas is prepared by heating ammonium nitrate. Outside the body it supports combustion, something like oxygen, but this is due to the dissociation of the nitrogen and the liberation of the oxygen. If a splinter of wood is ignited it is extinguished by the gas, but if the wood is well ignited sufficient heat is at once generated to produce the dissociation, and the gas then acts like oxygen.

In the living body it cannot be substituted for oxygen because the dissociation does not occur and asphyxia is produced. Both animals and plants placed in the gas die in much the same way as if they were in hydrogen gas.

Nitrous oxide is administered by inhalation to produce temporary anæsthesia during short operations. It was formerly believed that it acted only as an indifferent gas in the body, and that the anæsthesia was due to the oxygen being gradually replaced by the gas ; but this is very improbable. Bert has shown that if 80 parts of nitrous oxide and 20 parts oxygen are administered to animals at a pressure of $1\frac{1}{4}$ atmospheres, the effect as far as the nitrous oxide is concerned is the same as administering the pure gas, since the absorption of nitrous oxide depends upon its partial pressure in the lungs ; but also in this experiment as much oxygen is present as in air. The result is unlimited anæsthesia without asphyxia,

which shows conclusively that the drug does not produce its effect by depriving the body of oxygen. The nitrous oxide is dissolved in the blood, the amount taken up varying with the partial pressure ; it forms no chemical combination with any constituent of the body.

To produce satisfactory anæsthesia the last stage of inhalation must be conducted with the pure gas , for 80 per cent. nitrous oxide at atmospheric pressure only produces an imperfect anæsthesia. The asphyxia which supervenes is characterised by all the ordinary effects of the condition, but owing to the depressant action of the drug on the nerve-cells the convulsive movements are less marked than, say, when hydrogen or other indifferent gas is inhaled.

Nitrous oxide, therefore, acts in two ways :—(1) It depresses the central nervous system ; (2) it acts as an indifferent gas and induces asphyxia.

What is the nature of its action on the central nervous system we cannot yet say, but it is possible that its specific action may be the result of its greater solubility in fat and fat-like bodies, whereby the gas tends to collect in the central nervous system, and this tissue being more susceptible to small alterations in composition than others, depression and ultimately anæsthesia are produced.

The medullary centres would be depressed by the action of the gas. But the deprivation of oxygen during anæsthesia overshadows this effect, and results in the excitation of these centres. Therefore, respiration will cease sooner during the inhalation of nitrous oxide than of some indifferent gas. During the asphyxial stage the heart is slower, the blood-pressure rises from vaso-constriction, and respiration is deeper. The heart is not affected directly. Death occurs from lack of oxygen and not from the direct action of the drug.

During inhalation of a mixture of nitrous oxide and air the first stage is marked by subjective sensations. There are noises in the ears and indistinctness of vision. The patient soon loses control of himself, becomes excited and hilarious ; his movements and speech are inco-ordinated, and his gait staggering. The condition at this time resembles that of alcoholic intoxication.

This stage is succeeded by drowsiness and diminished sensibility to pain. When the pure gas is inhaled consciousness is quickly lost and signs of asphyxia, such as cyanosis, twitchings, irregularity and later cessation of respiration, are present.

If the mask is now removed the patient remains unconscious from twenty to sixty seconds. A recovery to the normal state occurs in two or three minutes, and there are no after-effects.

Nitrous oxide is much the safest anæsthetic we possess, but owing to the difficulty of prolonging the anæsthesia it is used almost exclusively in dentistry. The action of nitrous oxide exemplifies the law of dissolution. The highest centres are first depressed, and then the depression follows in the reverse order of development, the last part of the brain to be affected being the medulla.

The excitement stage is due to the depression of the controlling centres, whilst the lower centres, such as the motor area, are little affected.

If oxygen is inhaled with nitrous oxide the asphyxial symptoms are eliminated, but very profound anæsthesia cannot be obtained without increasing the pressure at which the gases are absorbed, unless doses of morphine and hyoscine have been previously given. In this way nitrous oxide produces anæsthesia under which major operations can be performed.

MATERIA MEDICA

Chloroformum. Dose, 1 to 5 m. (6 to 30 centimils).

PREPARATIONS

1. **Aqua Chloroformi.**—1 in 400.
   Dose, ½ to 2 oz.
2. **Linimentum Chloroformi.**—Equal parts of chloroform and camphor liniment.
3. **Spiritus Chloroformi.**—1 in 20 of rectified spirit.
   Dose, 5 to 20 m. (3 to 12 decimils) for repeated administration, **30 to 40 m.** (20 to 25 decimils) for a single administration.
4. **Tinctura Chloroform et Morphinæ Composita** contains chloroform, morphine hydrochloride, acidum hydrocyanicum dilutum (1 per cent. morphine hydrochloride).
   Dose, 5 to 15 m. (3 to 10 decimils).

Ether. Dose, 15 to 30 m. (1 to 2 mils), or **60 m.** (4 mils) may be given for a single administration.

PREPARATIONS

1. **Ether Purificatus.**—Ether from which most of the ethylic alcohol has been removed. Used as an anæsthetic.
2. **Spiritus Etheris.**—Ether, 1 part; alcohol, 2 parts.
   Dose, 20 to 40 m. (12 to 25 decimils) for repeated, **60 to 90 m.** (4 to 6 mils) for single administration.

Ether Aceticus. Dose, 15 to 30 m. (1 to 2 mils), or up to **60 m.** (4 mils) for a single administration.

HYPNOTICS

The hypnotics of the methane series are less volatile than the anæsthetics: they should be soluble in water so as to admit of rapid absorption. For convenience we divide them into three groups: (1) Chloral and its allies; (2) Sulphones; and (3) Urethanes.

I. CHLORAL GROUP.—**Chloral** is somewhat irritant, so that when rubbed into the skin it gives rise to a rubefacient effect. The

irritant effect may also show itself by nausea and vomiting when the drug is given by the mouth in a concentrated form.

It is to Liebreich that we owe our knowledge of the hypnotic effects of chloral hydrate, $CCl_3.CH(OH)_2$.

He suggested that its action was due to its decomposition by the alkalinity of the tissues and the formation of chloroform, thus :—

$$\underset{\text{Chloral.}}{CCl_3CHO} + \underset{\text{Sodium hydrate.}}{NaOH} = \underset{\text{Chloroform.}}{CHCl_3} + \underset{\text{Sodium formate.}}{H.COONa}$$

This is not the explanation of its action, as no chloroform is detected in the breath or tissues, and as the chloral can be regained from the urine.

Central Nervous System.—Chloral in moderate doses (10 to 30 grs.) produces a condition identical with natural sleep and lasting from six to eight hours ; the respiration and pulse are somewhat slower and the pupil is a little contracted as in sleep. In such doses it has no effect on the algesic areas, so that pain and other disturbing influences prevent the "chloral sleep" : in this respect it is in contrast to morphine. The spinal reflexes are not influenced in this stage.

When it is administered in larger doses (50 to 100 grs.) the patient falls into a deep sleep from which it is impossible completely to arouse him. Reflex action is weakened and sensibility to pain is diminished. There are also signs of medullary depression, as shown by the shallower respiration and fall of blood-pressure. Still larger doses produce complete anæsthesia and deep coma : there is general relaxation of all voluntary muscles and the reflexes disappear entirely. In profound sleep the amount present in the blood is probably somewhere about 0.03 per cent.

These effects are due to depression of the central nervous system, which first shows itself by a general diminution of objective perception, a diminished consciousness,* and so a tendency to sleep. The normal movements produced by electrical excitation of the motor area of the brain are diminished by even small doses of chloral, and after large doses the area does not respond to stimulation. The medulla is the last part of the central nervous system to be attacked. The effect here is shown by the respiration, which becomes progressively slower and shallower, and by the marked vaso-dilatation. The respiration is little affected by medicinal doses, not more than it is in normal sleep ; larger doses soon produce decided falling off in its activity, and death results from respiratory failure.

Circulation.—Chloral by depressing the medulla (vaso-motor centre) dilates the vessels : the vessels of the skin frequently show a well-defined dilatation, and, in consequence, skin eruptions

* Consciousness may be regarded as the sum total of perceptions at any one moment.

sometimes result ; these are generally erythematous, but sometimes purpuric or urticarial forms are seen. Any hypnotic may give rise to such eruptions. Chloral has a direct action on heart-muscle which, in its broad outline, resembles that of chloroform. When chloral is administered in medicinal doses we are dealing with a relatively small amount of poison acting over a prolonged period, whilst in the case of chloroform the poison is much more concen-

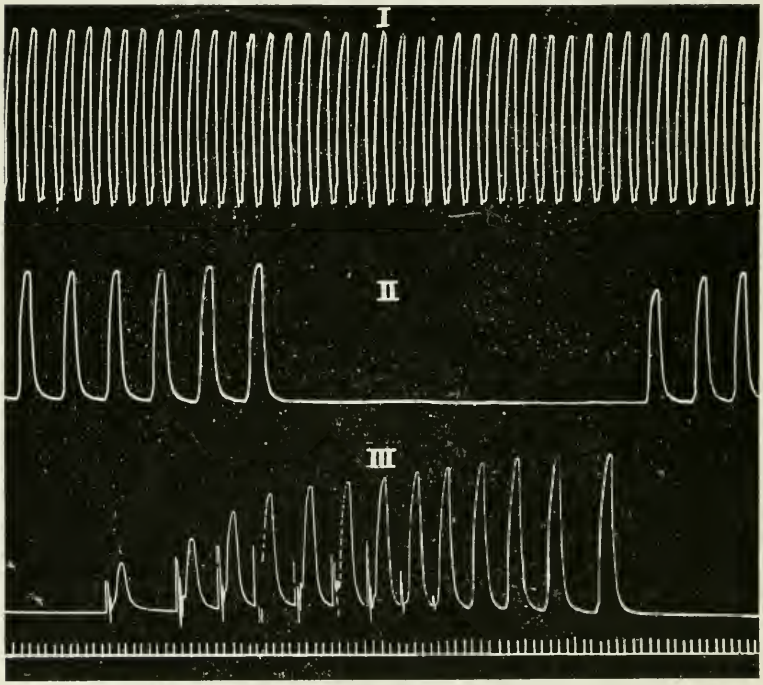


FIG. 7.—ISOLATED FROG'S HEART RECORDING BY THE METHOD OF SUSPENSION.

The heart is being perfused with a Ringer's solution through the hepatic vein. Upstroke = systole. I. shows the normal beat. II. shows the condition a quarter of an hour after perfusing with 1 in 5000 chloral : the heart is slower, the systole is much weaker, and the power of automatic contraction is beginning to go. III. shows the condition ten minutes later : automatic contraction is almost lost, but the heart still contracts to stimuli—the points of mechanical stimulation are shown by the irregular vertical lines. Time = secs.

trated but only acts for a comparatively short time. This poisonous action on the heart is only obvious when excessive doses have been administered. It is a perfectly safe hypnotic in medicinal doses but should be used in cardiac cases with great caution.

The blood-pressure falls both on account of the dilatation of vessels and the diminished cardiac output. Death from chloral almost always results from respiratory failure, although marked and even dangerous cardiac depression is not of uncommon

occurrence. Fig. 8 shows the action of a poisonous dose of chloral on the auricle, ventricle, and blood-pressure of the cat.

Other Effects.—Large doses of chloral produce a fall of temperature; this is due both to an increased loss of heat from the dilated skin-vessels, and to a smaller production the result of diminished muscular movements and depression of the basal ganglia of the brain in which the heat-centre is situated. Chloral has little or no action on muscle or nerve in the living animal; but in stronger solution, such as may be obtained by the direct application of the drug, it paralyses the nerve and sends the muscle into rigor (Fig. 9).

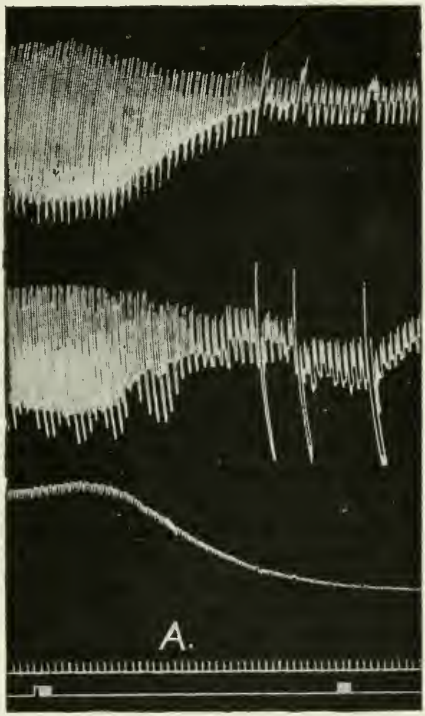


FIG. 8.—CAT. AURICLE AND VENTRICLE.

The tracing shows (1) movements of the right auricle, (2) movements of the left ventricle, and (3) B.P. The records were taken as in Fig. 4. At A a dilute solution of chloral hydrate was injected into the femoral vein. There is great cardiac depression affecting both the auricle and ventricle, and B.P. falls in consequence. Time = secs.

Chloral affects metabolism like chloroform. There is the same increased destruction of proteids, and the waste products are less completely oxidised than normally (*see* Chloroform). Less oxygen is absorbed during respiration and the carbonic acid output is diminished. Prolonged use of chloral has led also to fatty degeneration.

In the body chloral is mostly converted into trichlorethyl alcohol $C_2Cl_3H_2$-OH which acts like chloral; this combines with glycuronic acid and the resulting urochloralic acid is excreted by the kidneys. This body renders the urine very acid, and the metabolic changes, already mentioned, may be due to this acidity in the tissues, for all these changes can be prevented by giving the drug with alkaline carbonates. Urochloralic acid is formed principally in the liver and is non-poisonous. Glycuronic acid gives all the glucose reactions, but it does not permit sugar fermentation by yeast.

Prolonged abuse of chloral produces general depression, cachexia, and other symptoms similar to those seen in chronic alcoholism.

Butyl Chloral Hydrate ($CH_3CHCl.CCl_2.CH(OH)_2$) acts very similarly to chloral; it is a weaker hypnotic and does not produce cardiac depression to the same extent. Formerly, it was believed

to have a special action on the fifth cranial nerve, and was used as a specific in neuralgia; in reality it acts in this respect in no way differently from chloral.

With the object of overcoming the depressant action of chloral on the circulation, experiments have been conducted with a number of synthetical derivatives, two of which are mentioned.

Chloral formamide $\left(CCl_3CH\begin{matrix}OH\\NH.CHO\end{matrix}\right)$ is certainly less toxic to cardiac muscle than chloral, and, therefore, does not lower blood-

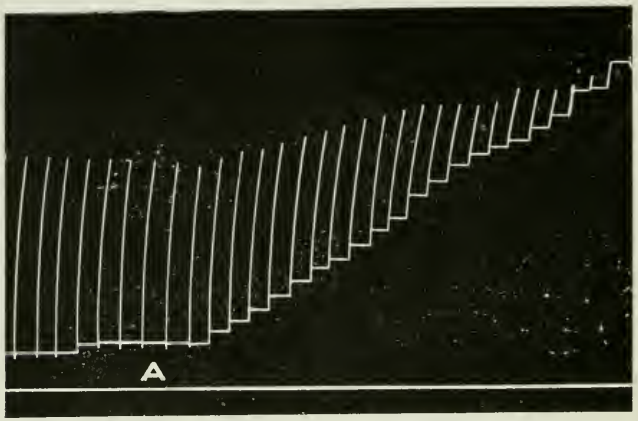


FIG. 9.—FROG'S GASTROCNEMIUS. ACTION OF CHLORAL.

Single induction shocks. Up to A normal: at this point 1 per cent. chloral was applied to the muscle, and death is shown in rigor. Stimulation was applied every fifteen seconds. Chloroform produces an exactly similar effect.

pressure to the same extent; but its hypnotic action is not so certain. Chloral formamide is decomposed in the body into formamide and chloral and is excreted as urochloralic acid. Sleep is produced in from one to two hours.

Chloralose is a compound of chloral and glucose:—

$$\underset{\text{Chloral.}}{CCl_3CHO} + \underset{\text{Glucose.}}{C_6H_{12}O_6} = \underset{\text{Chloralose.}}{C_8H_{11}Cl_3O_6} + H_2O.$$

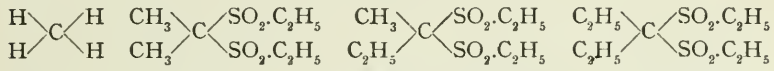
It is absorbed more slowly than chloral, but is a more powerful hypnotic. Unlike chloral it heightens reflexes, and in big doses may even give rise to strychnine-like convulsions. Why a combination of chloral with an inert sugar molecule should so greatly increase its narcotic effect and modify its action is almost incomprehensible on a pure chemical hypothesis, but can be understood on the assumption of some such physical hypothesis as that of Meyer.

Bromal Hydrate $\left(CBr_3CH\begin{matrix}OH\\OH\end{matrix}\right)$. Arguing from the soporific effects of the bromides, it was first thought that bromal would be

a more powerful soporific than chloral, but the Br ion is not produced and the bromal molecule acts as a whole. It is more toxic than chloral and there is excitement before the stage of narcosis.

Paraldehyde $(CH_3.CHO)_3$ acts like chloral, but has no depressant effect on the heart: it never gives rise to excitement, and on account of its volatility is more speedy in its action. Its only drawback is a rather unpleasant odour, which affects the breath for many hours, and a disagreeable taste. It is somewhat irritant to the alimentary canal. It acts in about fifteen minutes.

II. Sulphone Group.—The members of this class can be regarded as chemically allied to methane, in which all the hydrogens are replaced by alkyl and alkyl-sulphonic radicles.



Methane. Sulphonal. Methyl ethyl sulphonal (trional) known officially as methyl sulphonal. Diethyl sulphonal (tetronal)

The habitual use of these hypnotics does not lead to tolerance.

Sulphonal is a pure hypnotic and possesses no analgesic properties. It is less dangerous than chloral in that it has no depressant effect on cardiac muscle. It is absorbed very slowly on account of its insolubility, and should, therefore, be administered at least two or three hours before its effect is desired. The excretion of sulphonal is even slower than its absorption, so that the hypnotic effect is apt to be prolonged, and drowsiness is not uncommonly seen the day following its administration. Successive doses of sulphonal may give rise to poisonous symptoms from cumulative action. These show themselves by certain mental symptoms, such as confusion of thought and hallucinations, by gastritis, and by hæmatoporphyrinuria, caused by an iron-free product formed by the decomposition of hæmoglobin. This coloration of the urine is apparently due to a direct effect on the blood: it has been seen after the administration of sulphonal to anæmic women, and has also been obtained experimentally in rabbits.

Methyl ethyl sulphonal is more soluble and therefore more quickly absorbed than sulphonal, and hence its hypnotic effect is quicker.

Diethyl sulphonal is less soluble than trional. Both these drugs may produce, after prolonged use, the cherry-red urine due to hæmatoporphyrin (Fig. 69, p. 234).

The sulphones are very slowly decomposed in the body, and are excreted in the urine as ethyl-sulphonic acid, but a small amount is also excreted unchanged. The hypnotic action is due to the molecule as a whole, and not to the ethyl-sulphonic acid.

III. Group of Urea Derivatives $\left(CO\begin{matrix}NH_2\\R\end{matrix}\right)$.—Ethyl-urethane is the one generally used. They produce calm sleep, and have no depressant effect on the circulation. They are excreted as urea and so act as diuretics. Common urethane is a valuable anæsthetic for certain animals: about 1½ grams per kilo body-weight is required to produce deep anæsthesia in the rabbit.

Barbitonum $\left(\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\right)C\begin{matrix}CO—NH\\CO—NH\end{matrix}CO$ is another hypnotic which is generally safe. It forms soluble salts with alkalies. It may be administered in any hot drink. It is slowly excreted, so that prolonged effects of a single dose have been observed. In animals barbitonum may cause renal disease. The cumulative action appears to have been met with by many clinicians, and has given rise to much difficulty. Among the symptoms which it has produced are sickness and delirium, rash, giddiness, headaches, sweating, collapse. In acute poisoning besides coma, the spinal reflexes are increased and may lead to spasms (cp. chloralose). Barbitonum is absorbed and acts in about half an hour; it is very slowly excreted unchanged by the urine.

Tolerance can be acquired for any of these hypnotic drugs, and when it is produced for any one drug larger doses of any of the others are required to produce sleep. This is not true of the non-paraffinoid hypnotics; excessive doses of bromides are not necessarily required to produce sleep because tolerance has been acquired, say, against chloral. Barbitonum is known under the trade name of veronal and its sodium salt as medinal.

MATERIA MEDICA

Chloral Hydras. Dose, 5 to 20 grs. (3 to 12 dcgrms.).

Preparation

1. **Syrupus Chloral.**—Strength: 20 per cent. (weight in volume). Dose, ½ to 2 drs. (2 to 8 mils).

Butyl-Chloral Hydras. Dose, 5 to 20 grs.

Chloral Formamidum. Dose, 15 to 60 grs. Soluble to 5 per cent. in water.

Chloralose. (Not official.) Dose, 3 to 10 grs. Slightly soluble in water.

Bromal Hydras. (Not official.)

Paraldehydum. Dose, ½ to 2 drs. (2 to 8 mils). Soluble to 10 per cent. in water.

Sulphonal. Dose, 10 to 30 grs. (6 to 20 dcgrms.). Very slightly soluble in water.

Methyl sulphonal. Dose, 10 to 20 grs. (6 to 12 dcgrms.).

Dimethyl sulphonal. (Not official.) Dose, 10 to 20 grs. (6 to 12 dcgrms.).

Barbitonum. Dose, 5 to 10 grs. (3 to 6 dcgrms.).

Urethane. (Not official.) Dose, 1 to 4 drs.

THE MODE OF ACTION OF NARCOTIC SUBSTANCES

The mode of action of this group formerly presented great difficulties. As we have already seen, most drugs produce their specific effects by possessing a direct chemical affinity for this or that tissue, but such a simple explanation can hardly hold for the drugs now under consideration. In the first place, the alkyl radicle in these is not dissociated, and so it cannot interact with the constituents of the nerve-cells; secondly, the various members of the group do not possess any chemical characters in common; and, lastly, the physiological action has an incomprehensible relationship to the chemical constitution. A good example of the latter is offered by chloral and chloralose.

The only common factors to this vast group are apparently physical ones—a general power of diffusion into the uninjured cells of living tissue, comparative insolubility in water, and a greater solubility in fat-like compounds. On these common factors Hans Meyer has built up an hypothesis. If two non-miscible liquids, say oil and water, are placed in a vessel, and if a substance soluble in both is shaken up with them, this substance will dissolve in the two fluids in the proportion of its solubility in each: the proportion is spoken of as the partition-coefficient. The hypothesis supposes that in the living animal hypnotic substances dispose themselves in the same way. Now lecithin and cholesterin are the principal fat-like bodies with which we have to deal, and these are present especially in nervous structures; they, therefore, represent the oil in our experiment: the blood, lymph, and other tissues take the place of the water. The narcotic will thus pass into the lecithin and cholesterin-like constituents of the cell, and so change the physical conditions of this "brain lipoid" and interfere with the normal activity of the neurone. The anæsthetic action of a substance is, therefore, regarded by Meyer as a function of its solubility in fat or fat-like compounds, and the hypothesis may be spoken of as the partition-coefficient hypothesis. In support of this hypothesis it has been shown by many examples that all inert chemical substances which can diffuse into living cells and which undergo no change in the body are to some extent narcotic. This is true, for example, of such compounds as the mono-, di-, and trichlorhydrins, the triacetins, and many acid-amides.

Meyer and Overton have further shown that if a number of such bodies are obtained and their partition-coefficient estimated in water and fat-like compounds, then this figure gives an indication of their narcotic action. In the following table, where the partition-coefficient is in an inverse ratio to the amount of drug necessary to produce narcosis in tadpoles, this is seen:—

Name of Drug.	Partition-coefficient.	Amount of Drugs in Grams per Litre necessary to induce Narcosis in Tadpoles.
Trional (Methyl sulphonal)	4.46	.0018
Tetronal (Diethyl sulphonal)	4.04	.0013
Butyl-chlorate hydrate	1.59	.0020
Sulphonal	1.11	.006
Triacetin	0.30	.01
Diacetin	0.23	.015
Chloral hydrate	0.22	.02
Urethane	0.14	.04
Monacetin	0.06	.05

The most powerful narcotic substances are those which combine a very slight solubility in water with a very high solubility in olive oil or "brain lipoid."* The simplest method of determining the degree of narcotising action of a drug is to place tadpoles in different solutions of the drug; mammalians are quite unsuitable on account of differences in absorption and the impossibility of working under fixed conditions. The partition-coefficient is not easy to obtain and must be regarded as only approximately true for the temperature at which it is taken. If the narcotic is very soluble in one or other medium the law digresses.

This hypothesis alone cannot explain the action of the whole of this class of narcotic substances, but it is a very important factor to take into account when considering any individual member. Alcohol does not come into line with the hypothesis; it is miscible with water in all proportions, and is only slightly soluble in oil, and so should not tend to accumulate in nerve-cells. Alcohol is not strictly a member of the group because it is not inert; it exerts an action on proteins, and also it undergoes oxidation in the body. Alcohol, then, probably acts specifically and not in the same way as sulphonal. Chloral hydrate is also more readily soluble in water than in oil, and should be a much inferior hypnotic to sulphonal, but it is not. It is suggested, therefore, that chloral also has some action on the protein constituents of the nerve-cell; and many other exceptions might be given. Nitrous oxide is more soluble in oily substances than in water, and this physical property may be in some degree responsible for its anæsthetic action.

Traube has suggested that osmotic permeability is the most important physical factor necessary in a drug for the production of narcosis. By this must be meant the rapid penetration of the drug into the nerve-cells after absorption into the blood. Meyer says this penetration is due to the solubility of the drug in "brain lipoid," and Traube says that it is due to osmosis, which, in its turn, is due to the force of surface tension. So that according to Traube surface tension and narcotic power should run a parallel course.

* "Lipoid" is a term used to indicate fats or fat-like substances occurring in the organism which can be extracted by means of ether.

The narcosis is possibly due to the high concentration of the drug interfering with oxidation in nerve-cells.

The views given in this section should not be taken as a complete explanation as to how these drugs produce their effects, but they supply a useful hypothesis and represent a step forward towards a correct understanding.

Various physical hypotheses have been suggested to account for specificity of drugs on peripheral end-organs. The permeability of the cell, the solvent power of its limiting layer, and surface tension have each been suggested as possible explanations. Straub suggests that inhibition of the heart by muscarine is caused by the physical process of the passage of muscarine through the limiting layer of the cell, and that when it has passed this layer it cannot cause inhibition. He finds that in Aplysia muscarine is stored in the heart muscle, and that a certain amount in the outside fluid is necessary for inhibition. If this surrounding fluid is removed, the inhibition is removed. He found, further, in the Selachian heart that atropine delayed the absorption of muscarine, and suggests that atropine in some way alters the limiting membrane, so as to retard the absorption of muscarine below the threshold velocity necessary to produce an action.

This law does not necessarily hold in all cases, as, for example, the frog's heart, since muscarine may produce inhibition at a time when absorption must have ceased. But even supposing that a drug only acts in the course of its permeation into the cell due to a concentration difference inside and outside, this does not explain why strychnine, which is readily absorbed, does not cause inhibition. In other words, whilst physical factors may be of the greatest importance in limiting the action of a drug, they cannot be accredited with determining the specific type of action. It is difficult, for example, to explain on this hypothesis why adrenalin may cause either inhibition or contraction within the same class of tissue-cells, or why a nerve becomes paralysed as a result of giving a large dose of some stimulating poison.

Without entering into this question, we may take the broad view that drugs exerting a selective action on one or more tissues in relatively small doses (0.1 grm. or less in the case of man) do not tend to collect in the cells upon which they act more than in other cells, although there are exceptions, as in the case of the digitalis glucosides.

CHAPTER V

THE ACTION OF DRUGS ON NERVE-ENDINGS

When a drug produces some effect on an isolated organ the action may be either on the organ itself or on the nerve-ending in the organ. Thus, in Fig. 10, we may suppose the drug to act on the nerve-endings B or on the gland or muscle C. Exactly what this "nerve-ending" is we cannot say, but we know that there are in the organ at least three points upon which a drug can act, and as two of these actions correspond exactly with the effects obtained by exciting the nerve, we speak of such drugs as acting on the nerve-ending. The mechanism by which a nerve sets an end-organ into activity is at present hidden, but there is reason to think that the nerve-ending during activity liberates a chemical substance which by combination with some metabolite in the end-organ rouses it into activity. Thus vagal excitation stops the heart, because some muscarine-like body is liberated at the nerve-endings in the heart.

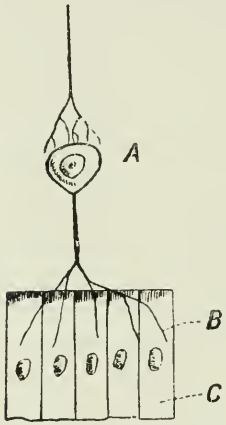


Fig. 10.—Diagram of Nerve-ending in a Secretory Gland or in Plain Muscle.

Drugs may paralyse or excite by acting on the nerve-cells, A; on the nerve-endings, B; or on the end-organ, C.

Without pursuing this subject further we proceed to classify the drugs which attack these endings. There are first the motor nerve-endings in striped muscle. These can be excited by either physostigmine or aconitine. The injection of either of these drugs into an animal produces spasmodic twitches in the voluntary muscles, which are peripheral since they are still obtained when the motor nerve is cut; they disappear after the injection of curare. Curare paralyses these motor-endings, because in a curarised animal excitation of the nerve has no effect on the muscle, whilst if the electrodes are applied directly to the muscle a normal contraction ensues. Drugs acting like curare are conine, methyl-

strychnium, and some others; they are of little importance in therapeutics.

A large number of drugs excite the nerve-endings in glands and plain muscle throughout the body. These drugs, therefore, produce salivation, sweating, cardiac inhibition, constriction of the pupil, augmented peristalsis, increased uterine, splenic, and bronchiolar contractions, vaso-constriction, &c. Some such drugs are muscarine, pilocarpine, and physostigmine. Colchicine also belongs to the same group, but it has comparatively little effect on glands and on the heart. Just as curare antagonises the action of physostigmine on striped muscle, so atropine and its allies antagonise the action of the drugs under consideration by paralysing the nerve-endings. The action of this group of drugs on the vaso-motor nerve-endings can be shown by their perfusion, first through the pulmonary vessels, and then through the splanchnic or systemic vessels. Now the pulmonary vessels are very feebly innervated and contain few nerve-endings, so that the drugs pilocarpine and muscarine produce little or no constriction of them, whilst they produce marked constriction of the ordinary systemic vessels.

Certain drugs pick out and excite only the sympathetic nerve-endings, and in particular we refer to adrenalin. This drug is considered elsewhere.

DRUGS DEPRESSING NERVE-ENDINGS

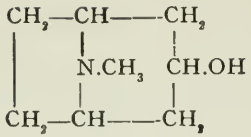
Belladonna, Stramonium, Hyoscyamus

Belladonna.—The dried leaves of *Atropa belladonna* (deadly nightshade) are official. The chief active constituents are the two optically isomeric bitter alkaloids hyoscyamine and atropine, the amount of which varies considerably, but is usually about 0.5 per cent., the greater proportion consisting of hyoscyamine.

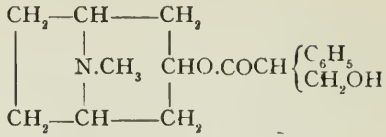
Stramonium.—The leaves and seeds of *Datura stramonium* are official. The principal active constituents are the two crystalline alkaloids hyoscyamine and atropine. Besides these there is a smaller quantity of a third alkaloid, hyoscine. The total alkaloid in the plant varies between 0.3 and 0.4 per cent.

Hyoscyamus consists of the dried leaves of *Hyoscyamus niger* (henbane). The chief constituent is hyoscyamine; there are also present small quantities of atropine and hyoscine.

Atropine is a combination of the base tropine with tropic acid and belongs to a class of bodies known as the tropeïnes. These tropeïnes are esters like ethyl-acetate; some occur in nature in plants of the Solanaceæ, and others are only formed in the laboratory.



Tropine.



Tropine. Tropic acid.

Atropine.

Tropine has none of the typical properties of atropine; in other words, as soon as the acid radicle is removed from atropine all its characteristic effects on peripheral nerve are absent. If, however, some aromatic acid is allowed to combine with it, a tropeïne is formed and the typical properties again recur. One of the most important of the artificial tropeïnes is that which contains the radicle of mandelic acid, viz. homatropine. Hyoscyamine behaves much the same as atropine and is isomeric with it. Hyoscine, though not isomeric, is very closely related. Atropine consists of a union of an equal number of molecules of the two optically active hyoscyamines.

Action

(1) *Stimulant action on the central nervous system.*

(2) *Paralysis of the terminations of certain nerves, especially those to secretory glands, plain muscle, and the heart.*

The action of atropine will be considered as representing a typical member of this group.

Local Action.—When applied to the skin atropine depresses the terminations of the sensory nerves. Any such effect, however, is small unless the drug is rubbed in with substances such as alcohol, glycerine, or fat, which aid absorption. Local application to the skin also results in some vaso-dilatation and in paralysis of sweat-glands. Atropine has been used therefore locally for the relief of pain in cases of excessive local perspiration, and to stop the secretion of milk. Sometimes after the prolonged application of a belladonna plaster sufficient atropine is absorbed to produce general poisoning.

In the mouth a small quantity of atropine is absorbed, and very shortly after the administration of the drug the mouth and throat become dry and there is difficulty in deglutition and articulation. In the stomach atropine also exerts a peripheral effect on the vagal nerve-terminals and dries up secretion. It is very quickly absorbed, partly from the stomach, but more rapidly from the duodenum, and produces its specific effects.

Central Nervous System.—The central nervous system is first stimulated and then depressed. This can be shown in both animals and man. In man, after a large dose, there are general excitement, restlessness, vertigo, talkativeness, laughter, and disturbances of vision giving rise to illusions generally of a pleasing character. These may be followed by delirium, mania, and in some

cases, when the dose is very large, by convulsions. After a varying period of excitement drowsiness develops, followed by sleep, which passes on insidiously to coma; death ultimately ensues from respiratory failure.

It will be observed that the picture here drawn is not very unlike that in alcoholic poisoning, in which the stage of excitement is the result of depression of the highest centres. But the action of atropine cannot be explained in this way, because there is evidence of direct stimulation: (1) an increased activity of the medullary centres, as shown by the stimulation of respiration and the vaso-constriction of central origin; (2) an increase of reflexes; (3) the fact that the motor area is more readily excited by electricity; and (4) the psychical centres are not depressed after small doses. We must therefore regard the action as a true stimulation that affects particularly the motor areas of the brain, which are rendered so excitable that the controlling centres can no longer hold them in check. The excitation is evident only to a less degree on the higher centres and cord. In the frog, where the brain is very poorly developed, the main action is on the cord: the voluntary and respiratory movements soon cease, and later a paralysis of motor nerve-endings occurs. This is followed, in two or three days, by a stage of increased reflexes and clonic convulsions. Respiration returns and the animal eventually recovers.

Atropine is used in therapeutics as a stimulant to the brain and medulla in conditions of depression.

Secretory Glands.—Nearly all the secretions are diminished as a result of paralysis of certain nerve-endings. In the case of the salivary glands atropine paralyses the chorda tympani so that stimulation of this nerve produces no secretion even when the electrodes are pushed down into the hilus of the gland—that is to say, the paralysis is peripheral to the nerve-cells on B or C in Fig. 10. But the gland-cells themselves are unaffected, because sympathetic excitation still gives rise to secretion, and hence the drug must act on the peripheral nerve-endings (Fig. 11). Excitation of the chorda also results in vaso-dilatation, but atropine, while picking out and paralysing the secretory fibres of this nerve, leaves the vaso-motor fibres intact. The glands in the mouth, throat, nose, and respiratory passages are affected similarly. The gastric and intestinal glands are controlled largely by nerve-impulses carried by the vagus, and this influence would be eliminated by atropine. In the same way the secretory nerve of the pancreas, which is very poorly developed, is paralysed; but pancreatic secretion, the result of taking food, is not affected directly, because the flow of juice is not nervous, but due to the absorption of secretin, a body which acts directly on the gland-cells.

A similar type of paralysis is induced on the terminations of the nerves to the sweat-glands; so that stimulation of the sciatic nerve in dogs and cats after the administration of atropine produces

no perspiration on the pads of the feet. The effect on the glands of the skin may also be shown readily in the frog, the skin of which becomes dry a few hours after receiving a small injection of atropine. The action on the secretion of bile and milk is more uncertain, but the secretion is stated to be diminished in each case.

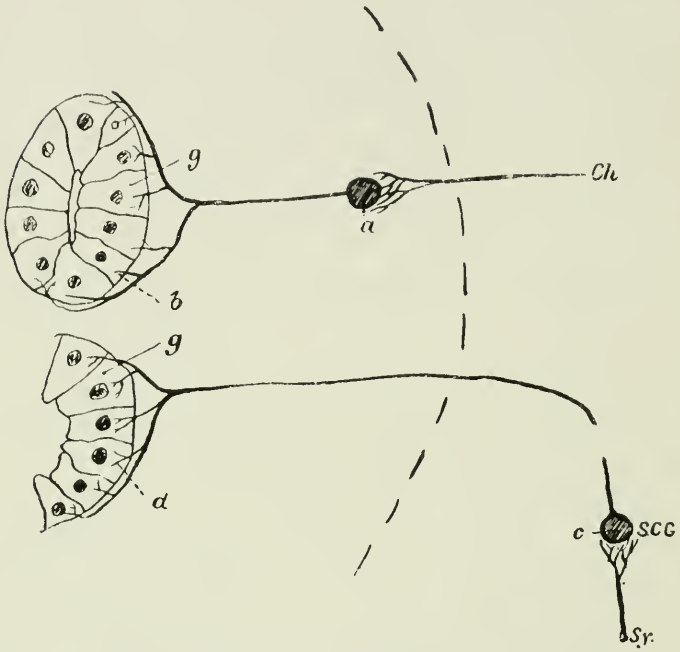


FIG. 11.—DIAGRAM SHOWING THE DIFFERENT POINTS OF ACTION OF DRUGS ON THE SUBMAXILLARY GLAND. REFLEX EFFECTS ARE NOT SHOWN.

g = gland-cell; *Sy* = sympathetic nerve; *SCG* = superior cervical ganglion; *d* = nerve-endings in the gland; *Ch* = chorda tympani; *a* = nerve-cells and *b* = nerve-endings in the gland. The dotted line represents the periphery of the gland.

POINT OF ACTION OF DRUGS.

a and *c*.	*b*.	*d*.	*g*.
Nicotine + -	Pilocarpine +	Adrenalin +	Certain metals,
Coniine + -	Physostigmine +	Cocaine +	particularly
Lobeline + -	Muscarine +		Mercury +
Gelsemine -	Atropine -		
Codeine -	Hyoscyamine -		
Curare -	Hyoscine -		
Sparteine -			

(+ represents stimulation and - depression.)

Atropine is employed in medicine to diminish secretion from the sweat and mammary glands.

Plain Muscle.—It will be convenient to describe first the action on the pupil. It is obvious from a reference to Fig. 12 that the condition of the pupil depends on the relative tendency to contraction of the two opposing muscles in the iris, the circular (*m*) and radiating (m_1).

A.—Radiating Muscle Fibres.

(1) Sympathetic centre.
(2) Superior cervical ganglion (*d*).
(3) Nerve-endings in muscle (*e*).
(4) Muscle (m_1).

B.—Circular Muscle Fibres.

(1) Centre for ocular motor nerve (*a*).
(2) Ciliary ganglion (*d* III).
(3) Nerve-endings in muscle (*c*).
(4) Muscle (*m*).

Stimulation of the circular muscle or any of its nervous mechanism as in (B), or paralysis of the radiating muscle under (A), results in constriction, and *vice versa*.

Atropine induces wide dilatation of the pupils, which will react

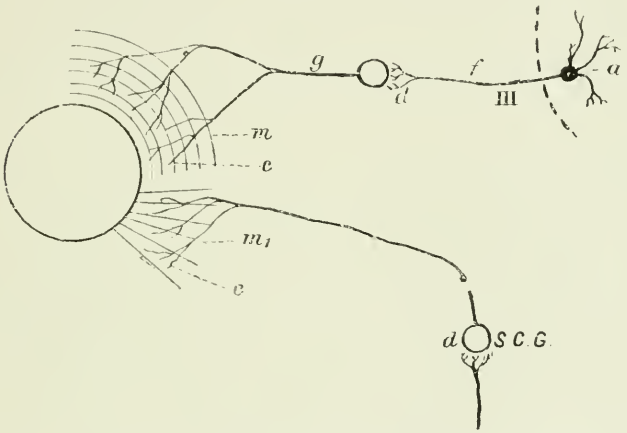


FIG. 12.—DIAGRAM SHOWING THE ACTION OF DRUGS ON THE PUPIL.

III = third nerve, *f* being the pre-ganglionic part and *g* the post-ganglionic part; *a* = nerve-cell in medulla and *d* in the ciliary ganglion; *e* = nerve-ending in the circular muscle *m*; *S.C.G.* is the superior cervical ganglion, the cells of which, *d*, terminate at *e* in the radiating muscle m_1. of the iris.

POINT OF ACTION OF DRUGS.

d.	*c.*	*e.*	*a.*	*m* and m_1.
Nicotine + −	Pilocarpine +	Adrenalin +	Morphine − + ?	Barium +
Coniine + −	Physostigmine +	Cocaine +	Cannabis Indica −	Veratrine +
Lobeline + −	Colchicine +		Hypnotics	
Gelsemine −	Muscarine +			
Curare −	Atropine −			
Sparteine −	Hyoscyamine −			
	Hyoscine −			

(+ represents stimulation and − depression.)

no longer to light. This action is local because it is obtained readily on the excised eye, and further, if the application of the drug is limited to one side of the eye, dilatation is observed only on that particular side, the rest of the pupil remaining contracted. If the motor oculi is excited in an atropinised animal either centrally (*f*) or peripherally (*g*) (Fig. 12) to the ciliary ganglion, there is no contraction of the pupil, but the muscle still reacts to electricity, so that paralysis of the terminals of the motor oculi in the circular muscle is proved. The dilatation is not maximal, since stimulation of the sympathetic gives rise to a further small dilatation. The

dilatation is of an active kind, and is due to the contraction of the radiating fibres when the circular have lost their tonus. This may be shown by fixing the iris in two places to the crystalline lens, when two bow-shaped dilatations will result. To explain this it is quite unnecessary to assume a stimulation of the radiating fibres or the nerves going to them, for the natural tonus is sufficient to account for the condition. In fact, the eye dilates for much the same reason that a limb becomes extended when all the nerves of the flexor muscles are severed. Excessive doses of atropine paralyse muscle as well as nerve-endings.

Accommodation is paralysed also and the eye remains focused for distance: this effect is the result of paralysis of the nerve-endings in the ciliary muscle; it begins after and passes away before the dilatation of the pupil. Intraocular tension is increased, as it usually is during dilatation of the pupil; the spaces of Fontana are so distorted that the exit of fluid from the chamber of the eye is hindered.

Intestine.—Small doses of atropine slightly increase peristalsis. Its action may be explained by supposing that it excites Auerbach's plexus, just as it excites the cerebral motor-cells and so allows reflexes to pass through more easily. But besides this it has another marked action; if much vagal tone is present, causing a condition of colic, such, for example, as is present during poisoning by pilocarpine and physostigmine, as well as in colic from other causes, atropine removes the excessive tonus without interfering with peristalsis. This may be a direct depression of vagal endings. The violent movements of the intestine induced by pilocarpine are antagonised by atropine without interruption of the path of the nerve impulse to the bowel. Nor is the bowel an isolated instance, for pilocarpine causes marked increase in the tonus of the retractor penis, which is abolished by atropine, yet the muscle continues to contract on stimulation of its nerve. The violent contractions of the rabbit's uterus under pilocarpine are arrested by atropine, though stimulation of the hypogastric nerves continues to be effective.

Atropine is largely prescribed with other purgatives to prevent griping. Griping is caused by intense local contractions of the gut arising from the reflex irritation of the purgative in the interior of the intestine: atropine probably relieves the condition by depressing some part of the peripheral vagal apparatus.

The peripheral ends of the vagi in the *bronchioles* are paralysed so that "asthma" (constriction of the bronchioles), whether produced reflexly through the nasal mucous membrane or directly by stimulation of the peripheral vagal endings, is cured temporarily by the use of this remedy; the bronchioles relax, and the volume of air entering and leaving the lungs is increased.

The *stomach*, *spleen*, *uterus*, and *bladder* behave in the same way as the intestines; colicky contractions are cut out, though the automatic peristaltic movements may be augmented.

Heart and Circulation.—Atropine paralyses the peripheral terminations of the vagus in the heart. This can be shown easily in the frog by placing on the recording heart a drop or two of a ½ per cent. solution of sulphate of atropine; in a few minutes neither stimulation of the vagi nor the sinus (stimulation peripheral to the nerve-cells) induces inhibition, although the inhibitory effects were reproduced typically before the drug was applied. In mammals small injections of atropine produce the same result: this paralysis of the peripheral vagal terminals, like section of the vagi, cuts off the tonic inhibitory influence of the centre and the heart is quickened. The increased rate will naturally only occur in those animals in which there is some tonic central effect. Thus the quickening is decided in dogs and little in cats, whilst in man it varies with the age and disposition, but is usually greatest between the ages of twenty-five and forty. In children under two months atropine causes no quickening, and it has also little effect in old age.

It is possible that besides this action atropine may directly stimulate cardiac muscle, since in minute amounts it slightly increases the automatic contractions of a strip of frog's ventricle. Any such effect, however, is of comparative insignificance.

When discussing the action of this drug on the central nervous system we alluded to the stimulation of the medulla. As a result of this we should expect to obtain (1) a slower pulse: this effect is neutralized completely by the peripheral depression of the vagi, nevertheless some cardiac slowing is seen occasionally in man soon after an administration of atropine, but is at most very transient; (2) a quicker and possibly deeper respiration; and (3) vaso-constriction.

Blood-pressure rises mainly as a result of this vaso-constriction, which is central in origin because the rise is much less after section of the cord. The pressure also tends to rise on account of the quickened heart; the output per beat remains about the same, but the output per minute is increased.

Constriction of vessels is pronounced only in the splanchnic area. The skin-vessels are dilated, and this is evident especially over the blush-area. Sometimes a rash appears on the face resembling that of scarlet fever, which may be followed in a day or two by desquamation. The dilatation of the vessels of the face is also central in origin, since it does not occur if the sympathetics in the neck are severed. The constriction of vessels in the splanchnic area in all cases overshadows any vaso-dilator effect produced in other parts of the body.

Dilatation of cutaneous vessels associated with constriction of the splanchnics is a not unusual effect with those drugs which excite the medulla.

Atropine is used in some cases of cardiac disease in which the pulse is very slow and irregular. It is also employed in the inhibitory stage of poisoning by digitalis and chloroform.

Respiration is slowed at first, but the excitation of the medulla soon causes it to become quicker and somewhat deeper. The initial slowing may be due to depression of the peripheral sensory vagal endings in the lungs, in which case the effect is analogous to that obtained on section of the vagi, and results from limiting the afferent impulses to the medulla. This is not the only cause, because an initial slowing may still be obtained when the drug is given after section of the vagi. It is more likely an effect due to dilatation of the peripheral bronchioles, whereby the resistance to the passage of air becomes less. Atropine is used largely in the treatment of asthma and in any condition in which it is desirable to excite the respiratory centre, as in poisoning by morphine and chloral.

Temperature.—It is not uncommon to find a small rise in temperature after taking a big dose of atropine. This is probably a direct action on the thermogenic centre in the corpus striatum. It cannot be due to a diminished loss of heat because the amount of heat dissipated is actually increased. In severe cases of poisoning the temperature rises sometimes very high, even to 107° or 108° F. It is this rise in temperature which is responsible for the vaso-dilatation of the skin-vessels : it is an attempt on the part of the nerve-centres to lower the temperature by increasing the loss of heat.

Idiosyncrasy Tolerance.—Herbivorous animals are very insusceptible ; rabbits, for example, can feed on belladonna leaves without injury, but when they are eaten by man they may induce symptoms of poisoning. The tolerance of rabbits is partly due to destruction of the alkaloid and partly to rapid excretion. Cats are very susceptible and they neither destroy it nor excrete it rapidly.

A mild degree of tolerance has been established in dogs. The salivary glands first become tolerant, and later the vagus and pupil. A local tolerance is said to be obtained for the pupil by the constant use of atropine drops (*see* chap. i.).

Excretion.—Atropine, like most alkaloids, is excreted in the urine. Its excretion is rapid, and the most delicate test of its presence is to instil a little of the urine into the eye of a kitten. Atropine may also be detected in minute quantities in the milk. After dilatation of the pupil, whether from internal administration or local application, the aqueous humour always contains traces of the alkaloid.

Small quantities of atropine can be oxidised in the body.

Symptoms.—If we piece these actions together we shall obtain a picture of the symptoms and signs observed after exhibition of the drug.

Large doses in man (about $\frac{1}{30}$ gr.) quickly produce a hot dry sensation in the mouth and throat, giving rise to thirst, difficulty in swallowing, and hoarseness in speaking. The flow of saliva ceases, the mouth, tongue, and skin become dry, and the face flushed. The pupils slowly dilate, vision becomes indistinct, and the respiration and pulse are quickened.

After still larger amounts there may be nausea and vomiting; the patient is quite unable to swallow though suffering from intense thirst, and the voice is stammering and incoherent. Vision becomes more and more disturbed and may even be completely lost.

Soon the effect of the drug on the central nervous system is in evidence. At first this is shown by restlessness, talkativeness, and garrulity, which give place gradually to delirium of an "imitative type" or to violent maniacal excitement. At this period twitchings of the face and limbs are sometimes observed, and even tetanic convulsions have been noted. The stage of excitement slowly passes off and is followed by depression. Sleep ensues, and gradually becomes deeper until coma is reached. Should paralysis affect the medulla, death will result from respiratory failure.

Hyoscyamine

Pure atropine and hyoscyamine act in the same way and with equal potency on the central nervous system in mammals. Atropine is more stimulant to the cord (frog) than hyoscyamine. Hyoscyamine is twice as powerful as atropine in its action on nerve-endings in the salivary glands, heart, and pupil. Now the action of atropine is the resultant of the action of equal amounts of *l*-hyoscyamine (natural alkaloid) and *d*-hyoscyamine; lævo-hyoscyamine is twelve to fourteen times as powerful as the dextro variety on the nerve-endings, but the dextro variety increases the reflexes. So that, speaking roughly, the pharmacological action of $\frac{1}{4}$ mg. atropine is equivalent to $\frac{1}{8}$ mg. *l*-hyoscyamine, the exaggerated reflexes which are induced in the frog by atropine being due to dextro-hyoscyamine.

Hyoscine

Hyoscine also closely resembles atropine in its peripheral actions, but it acts more powerfully, much more quickly, and the effects are of shorter duration. As little as $\frac{1}{450}$ gr. dilates the pupil in eighteen minutes, and this is followed soon by ciliary paralysis.

The stage of excitement is generally either very short or absent, and the second stage of depression is pronounced, showing itself soon after administration by drowsiness and a desire for sleep, so that this drug has come to be used as a hypnotic. It also differs from atropine in that there is no stimulant effect on the medulla, and no stage in which the excitability of the motor areas is increased to electrical stimulation.

The two active hyoscines which go to form common or racemic hyoscine bear the same relation to each other as the two hyoscyamines; the lævo-rotatory alkaloid is intensely poisonous to certain peripheral neurones, whilst the dextro-rotatory is almost devoid of action. Therefore *l*-hyoscine acts twice as strongly as the racemic base on peripheral nerve-endings. Both optical isomers act in the same way on the central nervous system.

It will be seen that the three drugs atropine, hyoscyamine, and hyoscine present a series in which the stage of excitement is marked

in atropine and almost absent in hyoscine, whilst hyoscyamine occupies an intermediate condition. On the other hand, hyoscine is much the most depressant and atropine the least so.

Injections of morphine and hyoscine have been used to produce general anæsthesia for operations. Complete anæsthesia can be produced also by morphine alone, but in this case the reflexes from the cord are pronounced and render the method objectionable. Anæsthesia by morphine-hyoscine is more dangerous than by the volatile anæsthetics. A preliminary injection of $\frac{1}{5}$ gr. morphine with $\frac{1}{200}$ gr. hyoscine is occasionally employed with volatile anæsthetics; it prevents the stage of excitement and allows complete anæsthesia to be obtained with a smaller amount of volatile anæsthetic. "Twilight sleep," a condition which is supposed to deprive labour of its terrors, is brought about by injections of morphine and hyoscine. The pains of labour are felt, but in a weakened form. After parturition the patient only vaguely remembers the suffering. The value of this treatment has yet to be determined.

Artificial Tropeïnes

Only one of these needs mention, viz. homatropine, which is a combination of tropine with mandelic acid. It has roughly the same action as atropine, but is considerably less poisonous. It is used almost solely for diagnostic purposes, to produce dilatation of the pupil during examination of the fundus of the eye. Its action after local application comes on and passes off much more rapidly than that of atropine. The local application of atropine dilates the pupils for two or three days; the effect of homatropine wears off in a few hours. Methyl-atropine salts also dilate the pupil in a few minutes, and the dilatation lasts only a few hours.

MATERIA MEDICA

BELLADONNA

Belladonnæ Folia (dried leaves). Must contain not less than 0.3 per cent. of alkaloids.

1. **Extractum Belladonnæ Siccum.**—1.0 per cent. of alkaloids. **Dose, $\frac{1}{4}$ to 1 gr.** (16 to 60 mgrms.).
2. **Tinctura Belladonnæ.**—Standardised to contain 0.035 per cent. of total alkaloids. **Dose, 5 to 15 m.** (3 to 10 decimils).

Belladonnæ Radix.

Preparations

1. **Extractum Belladonnæ Liquidum.**—Standardised to contain 0.75 per cent. of alkaloid.
2. **Emplastrum Belladonnæ.**—0.25 per cent. of alkaloids.
3. **Linimentum Belladonnæ.**—0.375 per cent. of alkaloids.
4. **Unguentum Belladonnæ.**—0.6 per cent. of alkaloids.
5. **Suppositoria Belladonnæ.**—Each contains $\frac{1}{60}$ gr. of the alkaloids.

Atropina. Dose, $\frac{1}{200}$ to $\frac{1}{100}$ gr. (0.3 to 0.6 mgrm.).

PREPARATION

Unguentum Atropinæ.—1 in 50.

Atropinæ Sulphas. Dose, like atropine.

PREPARATIONS

1. **Liquor Atropinæ Sulphatis.**—1 per cent. Dose, $\frac{1}{2}$ to 1 m. (3 to 6 centimils).
2. **Lamellæ Atropinæ.**—Each containing $\frac{1}{5000}$ gr. (0.013 mgrm.).

Homatropinæ Hydrobromidum. Dose, $\frac{1}{64}$ to $\frac{1}{32}$ gr. (1 to 2 mgrms.).

PREPARATION

Lamellæ Homatropinæ.—Each containing $\frac{1}{100}$ gr. (0.65 mgrm.) of homatropine hydrobromide.

STRAMONIUM

Stramonii Folia.

PREPARATION

Tinctura Stramonii. Dose, 5 to 15 m. (3 to 10 decimils).

HYOSCYAMUS

Hyoscyami Folia.

PREPARATIONS

1. **Extractum Hyoscyami** (standardised to contain 0.3 per cent. alkaloid). Dose, 2 to 8 grs. (12 to 50 ctgrms.).
2. **Pilula Colocynthidis et Hyoscyami.** Dose, 4 to 8 grs. (25 to 50 ctgrms.).
3. **Tinctura Hyoscyami.** Dose, $\frac{1}{2}$ to 1 dr. (2 to 4 mils).

Hyoscinæ Hydrobromidum. Dose, $\frac{1}{200}$ to $\frac{1}{100}$ gr. (0.3 to 0.6 mgrm.).
Hyoscyaminæ Sulphas. Dose, $\frac{1}{200}$ to $\frac{1}{100}$ gr. (0.3 to 0.6 mgrm.).
Agaricin (not official), obtained from the fungus **Polyporus.** Dose, $\frac{1}{4}$ to 1 gr.

Agaricin is an acid belonging to the malic acid series. It is employed to stop sweating, which it does without causing dryness of the mouth or throat. The explanation of its action is not clear, since it affects all plain muscle in much the same way as strophanthus.

DRUGS EXCITING NERVE-ENDINGS

PILOCARPINE.—MUSCARINE.—PHYSOSTIGMINE.—COLCHICINE

PILOCARPINE

Jaborandi is the name given to the plant *Pilocarpus pennatifolius*. From Jaborandi leaves the following alkaloids can be extracted:—

1. **Pilocarpine** ($C_{11}N_{16}N_2O_2$), which is in the Pharmacopœia in the form of the nitrate.

2. Pilocarpidine ($C_{10}H_{14}N_2O_2$), present in the leaves in only very small quantities. It has a weak pilocarpine action.

3. Isopilocarpine, present in only small quantity and acting like weak pilocarpine.

Action

Excitation of the Nerve-endings to Glands and Plain Muscle

Secretory Glands.—The secretion of the salivary, sweat, gastric, pancreatic, intestinal, mucous glands of mouth, nose, and respiratory tract, ceruminous and lachrymal glands, is augmented after the administration of this drug. The milk, bile, and urine are not decidedly influenced. The increased secretion applies both to the solids and watery constituents, but the increase in solid secretion is less in proportion than the increase of water.

The mode of action will be considered in detail in the case of the submaxillary salivary gland, as it is typically representative. In the first place, the increased secretion of saliva is not due to central stimulation, because it may be obtained when all the nerves are cut. Nor is it due to stimulation of the nerve-ganglia, because pilocarpine induces a big secretion when these are paralysed with nicotine; hence the drug must act either on the nerve-endings in the gland-cells or on the glandular cells themselves. If the nerve-terminals of the chorda tympani are paralysed by atropine, pilocarpine has no influence on the secretion, yet the glands themselves are unaffected, because electrical stimulation of the cervical sympathetic gives a typical increase of secretion; hence we must conclude that the drug stimulates the nerve-endings of the chorda tympani (Fig. 11).

The sweat is similarly increased. After a moderate dose, $\frac{1}{3}$ gr., the secretion begins on the face and neck and generally lasts after a single dose from three to five hours. In the cat, which sweats from the pads of its feet, pilocarpine induces secretion when the nerves are cut, showing that the action is not central. The effect is again antagonised by atropine, and hence one concludes that the seat of action is the peripheral "nerve-endings." There are certain conditions which present difficulties to this simple explanation. If pilocarpine is injected into people who have received some spinal injury, sweating only occurs above the area supplied by nerves from the affected part, whereas in the lower part of the body the sweating is slight or absent. The line of demarcation so produced is sufficiently definite to make such injections of use in the diagnosis of the position of cord-lesions. It is probable that such central lesions produce an inhibitory action on the sweat-glands. If the nerves to the cat's leg are cut and allowed to degenerate, pilocarpine still retains its action on the sweat-glands, so that the effect cannot be on the "anatomical nerve-endings."

The pancreatic secretion is increased very slightly: it is possible that this is due to the muscular contraction of the walls of the duct.

Bronchial secretion is shown by the rhonchi and crepitations which can be heard over the whole chest. The sugar in both the milk and blood is stated to be increased. Weight is reduced largely as a result of these effects.

The activity of the suprarenal glands is also increased as measured by the amount of adrenaline secreted into the circulation by the suprarenal vein.

Atropine in all cases antagonises the effect of pilocarpine on glands, and if sufficient atropine to paralyse completely the secretory nerves is administered first, no amount of pilocarpine can antagonise the effect.

Pilocarpine is said to increase the rate of growth of the hair.

Plain Muscle.—The motor nerve-endings to all plain muscle are stimulated, *i.e.* there are increased tonus and augmented automatic movements. This may be readily demonstrated on "ring

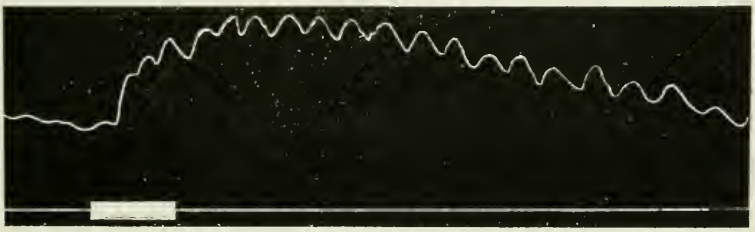


FIG. 13.—TRACING OF THE MOVEMENTS OF A FROG'S STOMACH.
At the indicated mark pilocarpine was applied, and the stomach immediately contracted and peristaltic-like waves were produced. Time, 1 cm = 1 min.

preparations" of the frog's stomach, to which the application of a little pilocarpine solution produces an effect, as seen in Fig. 13.

If the preparation is painted first with 0.05 per cent. cocaine solution, the pilocarpine induces no augmented contraction. The cocaine paralyses the nervous mechanism only, and does not affect the muscle because barium, which acts on this tissue, is still capable of producing its ordinary contraction. All plain muscle is affected in the same manner. As a result of the increased movements on the alimentary tract there may be nausea and vomiting, colicky pain and diarrhœa. The bronchioles are gradually constricted and the amount of air entering and leaving the lungs is enormously diminished; as the force of expiration is relatively insignificant in comparison with that of inspiration, the lungs soon become overdistended and a typical "asthma" is developed. Pilocarpine is sometimes employed in the treatment of asthma with beneficial results. This is not difficult to understand. The bronchioles are supplied by two sets of fibres, broncho-constrictors (vagus) and broncho-dilators (sympathetic). Pilocarpine excites the nerve-endings of both of these sets of fibres, and in the normal

animal broncho-constriction overshadows the inhibitory effect. But if for any reason the broncho-constrictor fibres have been in action some time so that the nerve-endings are fatigued, then excitation of the sympathetic or the administration of pilocarpine induces broncho-dilatation.

The effect on the bladder, uterus, and spleen is of the same nature as that on the intestines.

Pupil.—Pilocarpine contracts the pupil: this is readily shown by extirpating a frog's eye and placing it in a 1 per cent. solution in the dark. Therefore, the effect is peripheral, and as the sympa-

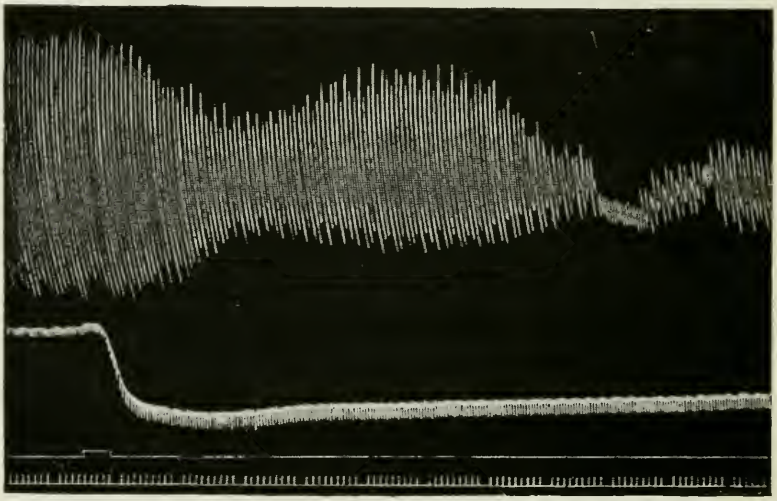


FIG. 14.—CAT, A.C.E. ACTION OF PILOCARPINE ON THE BRONCHIOLES.

Right vagus cut. Shows the effect of injecting 0.0075 grm. pilocarpine nitrate. Upper tracing = lung-volume, lower = B.P. Constriction of the bronchioles limits the air entering and leaving the lungs. The B.P. falls from cardiac inhibition. Both these effects are produced by excitation of the vagal endings. Time = secs. (Brodie and Dixon.)

thetic is not paralysed the action must be either upon the terminations of the third nerve or upon the circular plain muscle of the iris; but as the effect is eliminated entirely after a proper dose of atropine, whilst the muscle is still responsive to direct electrical stimulation, the point of action must be the nerve-terminals, Fig. 12 (*cf.* Physostigmine). The nerve-endings in the ciliary muscle are stimulated also, and the lens is, therefore, accommodated for short-distance sight. As a result of the contraction of the pupil intraocular pressure is diminished although there may be a transient initial stage of increased pressure.

Circulatory System.—The characteristic effect on the heart is well shown in the frog. The rate is diminished at once by pilocarpine, diastole is much prolonged and systole shortened; the effect is the same as that produced by stimulating the vagus with an

electric current. The seat of action is the terminals of the vagus, because if a weak solution of atropine is dropped on a heart previously slowed by pilocarpine the rate of contraction is quickly increased. The effect cannot be on the nerve-cells as at one time supposed, because pilocarpine slows the rhythmically contracting apex of the frog's ventricle, which contains none. Larger doses of pilocarpine may ultimately induce paralysis of the vagal terminals.

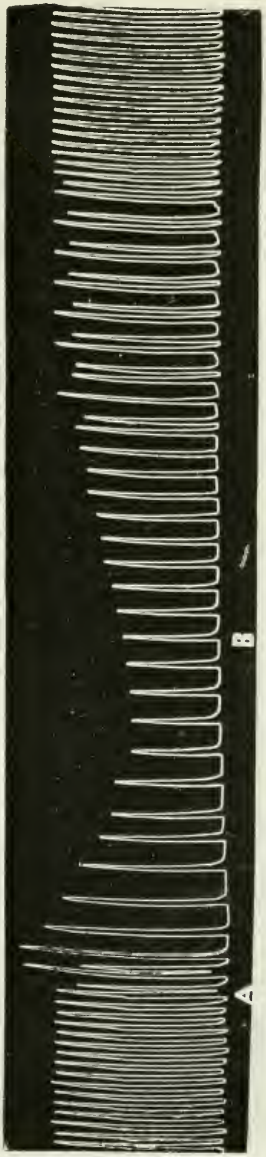


FIG. 15.—TRACING OF THE MOVEMENTS OF THE ISOLATED RABBIT'S HEART DURING PERFUSION THROUGH THE CORONARY VESSELS WITH RINGER'S SOLUTION.

At A a small dose of pilocarpine was added to the fluid, and at B this was replaced by atropine. It should be noted that the pilocarpine diminishes the force of systole and prolongs diastole: atropine completely antagonises the action.

The effect of intravenous injections in mammalia is similar to that already described. The heart is slowed by the peripheral vagal stimulation, and as a consequence of this, blood-pressure falls. Atropine immediately restores the former condition of affairs—that is, it quickens the heart; but the blood-pressure rises much higher than before, and this is due to the vaso-constriction induced by the pilocarpine, which is not antagonised by atropine.

The peripheral vessels of the body are dilated especially over the head and neck, but in the splanchnic area and in the limbs there is some vaso-constriction.

When pilocarpine is administered in small doses, either by the mouth or subcutaneously, some quickening of the heart occurs, and this is the usual therapeutic effect. Pilocarpine excites both the vagal and sympathetic endings in the heart. When the drug reaches the heart very slowly, as it does when it is given by the mouth, the sympathetic stimulation is dominant and the heart-beat quickens; whereas, when the dose is large or when the pilocarpine is injected into the circulation, the vagal action is dominant and the heart is slowed (Fig. 16).

The action of pilocarpine on the sympathetic endings induces vaso-constriction. This is best shown by perfusing some organ

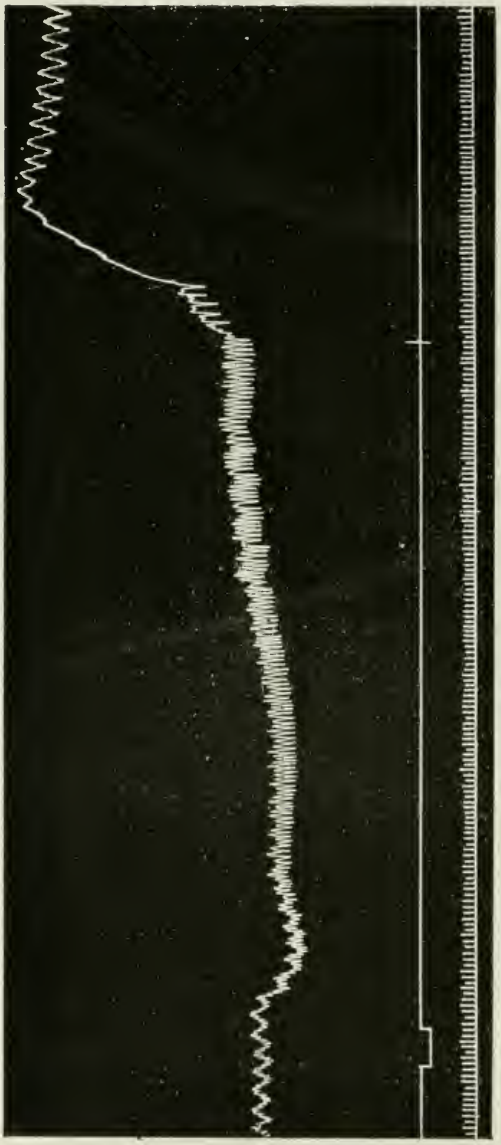


FIG. 16.—DOG, B.P.

At the first mark pilocarpine 1 c.c. 0.3 per cent. was injected into the jugular vein. The heart is slowed and B.P. falls at first, but the vaso-constriction also induced by the pilocarpine keeps the pressure up in spite of the slowing. At the second mark atropine 1 c.c. 0.1 per cent. was given, and the heart becomes very rapid—much quicker than it was in the normal condition; in consequence B.P. rises considerably. Atropine removes not only the effect of the pilocarpine but all the normal tonic inhibitory impulses. Time = secs.

such as the intestines or kidney, and it will be found that when a little of the alkaloid is added to the perfusing fluid the outflow from the vein is decidedly and rapidly diminished. Therapeutic doses

of pilocarpine, therefore, tend to raise blood-pressure: (1) because the heart is slightly accelerated; (2) because of vaso-constriction.

Blood.—Pilocarpine gives rise to a lymphocytosis—that is, it increases the number of those white corpuscles in the blood which are derived from the spleen and lymphatic glands. Lymphocytosis is quite distinct from ordinary leucocytosis, which is pro-

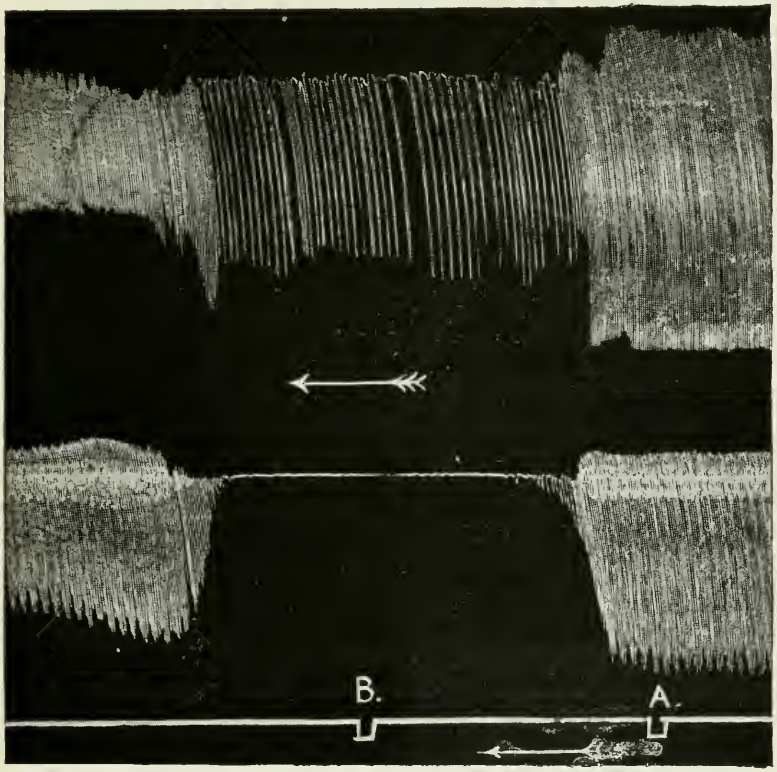


FIG. 17.—DOG. MOVEMENTS OF VENTRICLE (UPPER TRACING) AND AURICLE (LOWER TRACING).

At A a small injection of muscarine was given, and the vagal inhibitory fibres were powerfully excited, so that the auricle was completely inhibited in diastole, and the ventricle beat very slowly and irregularly. At B atropine was injected into a vein, and the effects of inhibition passed off. Pilocarpine produced an effect very similar to that of muscarine.

duced by such substances as colchicine and is the expression of a chemiotactic action. It has been shown that the action of the drug on the involuntary muscle of the spleen and lymphatic glands resulting in their constriction may be responsible for this lymphocytosis; it is a mechanical action whereby the white cells are squeezed out.

The specific gravity of the blood is considerably increased by the loss of fluid from the tissues.

Central Nervous System.—These effects are quite insignificant and are overshadowed entirely by the peripheral actions. In frogs pilocarpine gives rise to convulsions, and in mammalia slight convulsive movements may be seen, especially if the drug is injected intravenously. Muscular weakness of central origin develops in the later stage. These effects are of little importance, except in cases of poisoning.

Symptoms.—We are now in a position to examine the symptoms which will ensue from a dose of pilocarpine whether given by the mouth or subcutaneously. Marked salivation, perspiration, and flow of tears are soon evident. The sweating begins on the face and together with the salivation lasts from three to five hours. The pulse and respiration are quickened. With larger doses nausea, vomiting, painful colic, and profuse watery diarrhœa ensue. The pupil is contracted and the pulse may now be slow. Respiration becomes dyspnœic and rhonchi are heard all over the chest, a result of the free secretion from the bronchial mucous membrane. The chest is over-distended and exhibits all the characteristics of an attack of spasmodic asthma, which indeed is practically what is present. Tremors, convulsions, and muscular weakness may occur later, and death results from asphyxia.

Muscarine has much the same action as pilocarpine. It stimulates the same nerve-endings, but the stimulation of the cardiac vagus and of involuntary muscle is generally of a much more intense character. Certain cases of fungus poisoning are due to this body, and in these the characteristic symptoms consist of violent vomiting and diarrhœa, asthmatical respiration, followed by coma, convulsions, and death. Arecoline, an alkaloid from the areca-nut, has a similar action.

PHYSOSTIGMINE

Calabar Beans are the ripe seeds of *Physostigma venenosum*. They contain about 0.25 per cent. of an alkaloid *physostigmine* or eserine, as well as two other alkaloids which are probably decomposition products of physostigmine. They are *calabarine*, which is present in only minute quantities and has a strychnine-like action in frogs, and *eseridine*, which is similar in action to physostigmine but less toxic. Physostigmine differs from pilocarpine in that it exerts a stimulant effect on nerve-endings going to striped muscle, a more pronounced action on the peripheral blood-vessels, and a direct effect on cardiac muscle. Physostigmine and pilocarpine resemble one another in their action on involuntary muscle and on secretory glands.

Striped Muscle.—Physostigmine gives rise to peculiar tremors or fibrillary contractions of striped muscles: they begin in the hind limbs and later spread to all the muscles. These tremors are peripheral in origin, as they are still evident after section of the nerve

going to the part; but if the motor nerve-endings are paralysed completely with curare they disappear. One must conclude, therefore, that the action of this drug is on the peripheral nerve endings: their irritability is heightened to such an extent that at last they discharge stimuli automatically into the muscles. Sometimes these twitchings are so severe as to simulate convulsions. Curiously enough, the tremors are also antagonised by atropine and calcium, neither of which drugs apparently affects the motor nerve-ending.

Physostigmine also exerts an action on the muscle-fibre because its irritability remains exaggerated even after curare; that is to say, a smaller stimulus than before is required to produce an equal contraction. The working power of the muscle is also said to be augmented.

Plain Muscle.—It will be convenient to examine the action of physostigmine on the eye in some detail, partly because it has received so much attention, and partly because the effect may be taken as typical of that upon other plain muscle.

When the alkaloid is applied directly to the conjunctiva it causes great constriction of the pupil. This effect is local, because it can be produced after cutting all the nerve-fibres or by immersing a freshly excised eye in a dilute physostigmine solution. As the sympathetic nerve is not paralysed or otherwise affected the constriction must be the result of stimulation of the nerve-endings of the motor oculi, or a direct effect on the muscle of the iris, and both these views are still held. There can be little doubt that the constriction is the result mainly of peripheral nerve-stimulation, and this for two reasons:—(1) If all the ciliary nerves are cut and allowed to degenerate completely physostigmine produces no contraction, although the muscle of the iris is intact, as can be shown by its response to electrical excitation and certain drugs; (2) after the application of a large quantity of atropine to the eye, so that the pupil is widely dilated, physostigmine fails to produce any effect, although the muscle can be shown to be unaffected. Physostigmine also stimulates the nerve-endings in the ciliary muscle and produces a spasm of accommodation. The intraocular pressure is considerably reduced as a result of the contracted pupil. This is due to widening of Fontana's spaces caused by the concentric movement inwards of the ciliary body so that the movement of vitreous humour outwards is facilitated. Anderson has shown recently that if the ciliary ganglia be removed completely from animals, after a few weeks' rest the local application of physostigmine to the eye produces no contraction of the pupil, whilst pilocarpine induces decided contraction. This can only mean that the body or metabolite upon which the physostigmine acts is absent, whilst that acted on by the pilocarpine is present. The two alkaloids do not bring about their action in an identical fashion. Nevertheless physostigmine is not without effect on such an eye,

for after its application, although the pupil does not contract, the light reflex returns. This may be an effect on muscle-irritability analogous to that induced by the drug on striped muscle.

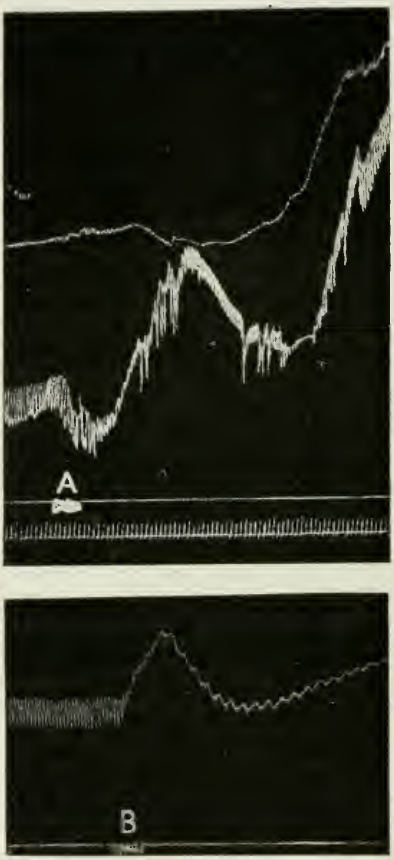


FIG. 18.—CAT. INTESTINAL VOLUME AND B.P.

At A a small injection of physostigmine was made into the jugular vein. The B.P. rose from vaso-constriction. The figure also shows a second sudden rise in pressure due to the onset of convulsive tremors and to liberation of adrenaline. The lower tracing shows the B.P. only, some minutes later. Atropine was administered at B, when the heart beat more rapidly and the pressure rose and tremors ceased. Time = secs.

These facts can be interpreted on the assumption that pilocarpine acts more peripherally than physostigmine.

All other plain muscle is affected in much the same way. Vomiting is common, a result of the increased gastric movements. Peristalsis is exaggerated, food is hurried along, therefore no time is allowed for the absorption of fluid, and so a watery diarrhœa occurs. The automatic bladder movements are augmented and the tone increased. The bronchioles constrict, the uterus and gall-bladder also show increased automatic movements. That the effect in all these cases is local can be shown by the direct application of the drug to the part, when in each case contraction of the plain muscle results. Here, as in the case of pilocarpine, the effects are antagonised by atropine.

Secretions.—All the secretions are increased in much the same way as with pilocarpine. The submaxillary gland may be taken again as a typical example. Physostigmine when injected into a vein gives rise to an immediate increase in the rate of secretion. This is not due to central or reflex mechanisms, because it occurs after section of the nerves. Neither is it an effect on ganglionic cells, because the increased secretion may still be obtained when these are paralysed with nicotine. The action must therefore be on the gland-cells or on the peripheral nerve-endings. But if the nerve-terminals are paralysed completely by a large dose of atropine, physostigmine fails to produce any secretion,

i.e. both these drugs affect some part of the endings of the chorda tympani, and there is reason to think that the seat of action of atropine is more peripheral than that of physostigmine. Smaller amounts of atropine may so affect the chorda tympani that while electrical excitation gives rise to no secretion, physostigmine in

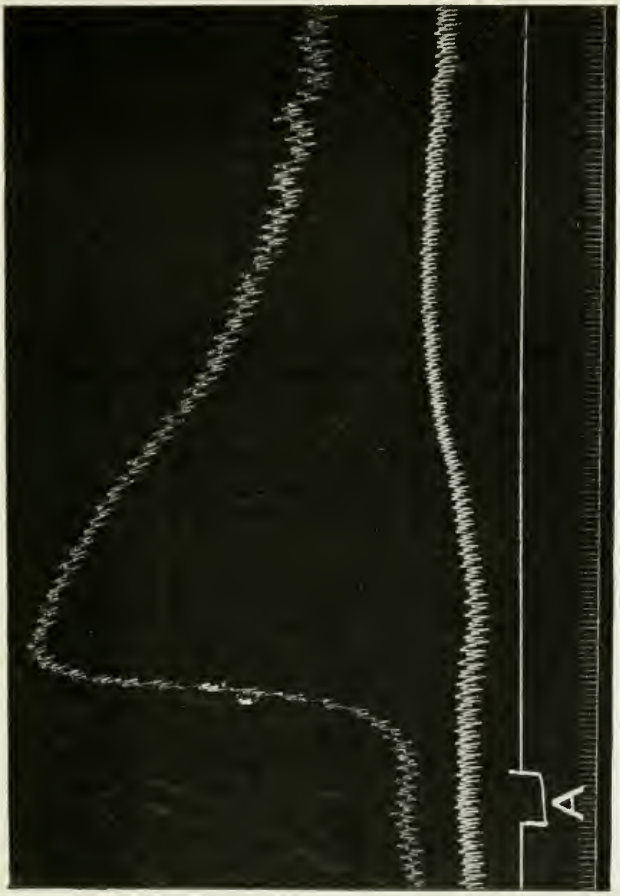


FIG. 19.—DOG (DECEREBRATE). PULMONARY PRESSURE AND B.P.

Upper tracing = pulmonary press. in mms. of half-saturated saline solution; lower tracing = B.P. in mms. of mercury. At A a small injection of physostigmine was given by the femoral vein. The B.P. soon rose, and the heart-beat, which was at first slightly accelerated, later showed the typical slowing. The pulmonary pressure showed an immediate and very decided rise, probably from constriction of the pulmonary vessels—the drug reaching these vessels before the systemic. Time = secs.

large amounts not only induces a secretion but removes the effects of the atropine, so that electrical stimulation once again gives rise to a secretion of saliva.

Hence these two drugs are to a certain extent mutually antagonistic, but the antagonism of atropine to physostigmine is much greater than that of physostigmine to atropine. Both the solid and liquid parts of the secretion are increased, but the increase of the water is greater in proportion than that of the solids.

The sudoriferous pancreatic mucous suprarenal and lachrymal glands are affected similarly, but the milk, bile, and urine are probably not altered.

Circulation.—The effect on the circulatory system is a little different from that of pilocarpine. In the frog the direct application of physostigmine to the heart results in a slower and stronger beat. This is mainly the result of a direct effect on the heart-muscle, as it can still be obtained after the vagal terminals have been paralysed with atropine. Indeed, in the case of the frog the vagus appears to be depressed rather than stimulated, since vagal excitation produces no cardiac slowing after the application of a 1 per cent. solution of physostigmine to the heart.

In mammalia the pulse-rate is slowed also, and the blood-pressure is raised. The slowing is due partially to vagal stimulation, because if the weakest faradic current which, applied to the vagus, induces inhibition is determined, and if then physostigmine is injected, a weaker current will give the same effect. This is only the case with small doses of physostigmine; larger amounts, as in the frog, depress the vagal endings. This is not the only cause of the slowing, since, as in the frog, it is still obtained when the vagi are paralysed with atropine, and hence there is either a direct action on cardiac muscle or a depression of the sympathetic (accelerator) endings.

The rise of blood-pressure is the result of vaso-constriction: it is mainly peripheral, as constriction of vessels can be seen in a loop of intestines after section of both splanchnic nerves. If a loop of gut or the limb of a cat is perfused artificially, the addition of a small amount of physostigmine to the perfusing fluid produces an immediate diminution in the outflow. This effect can be obtained also, after perfusing the pulmonary vessels, so that some portion (probably most) of its action on vessels is a direct one on the muscle-fibre.

Central Nervous System.—When injected into either mammals or frogs, muscular weakness and loss of reflexes are two of the characteristic effects obtained, and they result from depression of the central nervous system. The depression begins in the lower centres (cord) and spreads upwards, so that consciousness is preserved until the end. In the cat some excitement follows injections of physostigmine, and this has led to the statement that there is an initial stage of stimulation.

Physostigmine, then, differs from pilocarpine in its action on peripheral structures in the following ways: (1) It increases the irritability of nerves, rendering them more responsive to stimulation; pilocarpine is much less effective in this respect, but it has a greater action on the peripheral tissue. Pilocarpine acts more peripherally than physostigmine. (2) Physostigmine increases the irritability of the motor-nerves, leading to irregular muscle-twitchings. (3) Physostigmine has a direct action on all muscle tissue, which is rendered more irritable.

Certain ptomaines—choline, neurine, spermine, and some others—might be classified in this group; they have no therapeutic importance.

MATERIA MEDICA

Pilocarpinæ Nitras.

Dose, $\frac{1}{120}$ **to** $\frac{1}{5}$ **gr.** (3 to 12 mgrms.).

CALABAR BEAN

Physostigminæ Sulphas.

Dose, $\frac{1}{64}$ **to** $\frac{1}{32}$ **gr.** (1 to 2 mgrms.).

Preparation

Lamella Physostigminæ.—Physostigmine sulphate, $\frac{1}{1000}$ gr. (.065 mgrm.) in each lamella.

COLCHICUM

Colchicum corm is the underground stem of the meadow saffron, *Colchicum autumnale*. The active constituent of the drug is the alkaloid colchicine, of which it contains about 0.5 per cent. Colchicum seeds contain more colchicine, 0.5 to 1 per cent.

When the drug is taken by the mouth it gives rise at once to certain symptoms comparable with those produced by pilocarpine. It excites the same mechanism in plain muscle and in glands. The first effect is an increase of the peristaltic movements of the intestines, and therefore the first signs to be observed are generally vomiting and diarrhœa. These effects are produced in exactly the same manner as they are with pilocarpine, and they are abolished by the administration of a little atropine. The other forms of plain muscle are affected in the same way; increased automatic movements and increased tonus are seen in the spleen, uterus, and bronchioles.

The nervous mechanism to glands and to the heart is also excited a little, but to nothing like the same extent as with pilocarpine; and, indeed, when the drug is given by the mouth the glands and heart-rate remain practically unaltered.

Colchicine exerts a further more insidious and remarkable action on the central nervous system after a latent period of from three to six hours. No matter how the drug is administered, subcutaneously, by the mouth, or into a vein, nor in what doses it is given, these symptoms cannot be induced sooner. In this respect this most remarkable "slow poison" resembles the toxins. Now the toxins, so long as they remain in the circulation, do not influence the nerve-cells: they are absorbed by the peripheral neurones and gradually pass along the axis cylinders to the nerve-cells. It is possible that this is the explanation of the slow action of colchicine. At all events, after this latent period a motor and sensory paralysis

gradually supervenes, and death ultimately ensues from respiratory and vaso-motor failure.

Jacobi has shown that colchicine becomes changed to oxydicolchicine both by the slow action of air and light and by nascent oxygen. He further showed that when it is perfused through the kidney it rapidly undergoes a similar change. He concludes that the oxidation occurs normally in the living body.

Colchicine is only very slightly toxic to frogs, but oxycolchicine is very toxic: the activity of the drug would seem to be due to oxydicolchicine, which, in the case of cold-blooded animals, is not produced

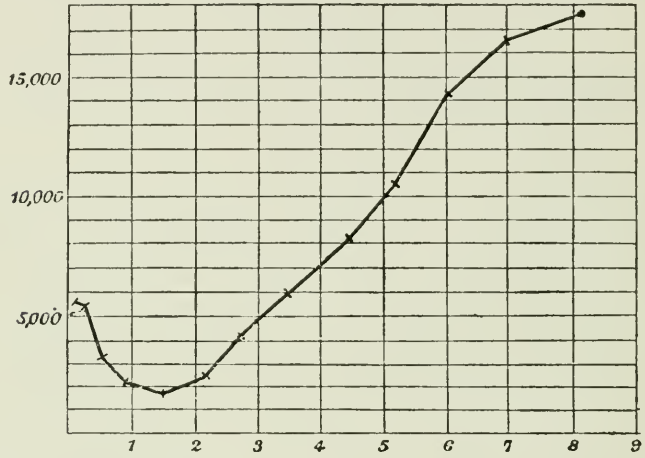


FIG. 20.—GRAPHIC REPRESENTATION OF THE NUMBER OF LEUCOCYTES IN THE PERIPHERAL CIRCULATION OF A RABBIT.

Ordinates = number of leucocytes, abscissæ = time in hours. The average number at first was 5500. Colchicine 0.006 grm. was then given subcutaneously, and after a short stage of hypoleucocytosis the leucocytes rapidly increase, reaching a maximum in about twelve hours. If taken by the mouth the effect is much diminished.

in the body from colchicine. If a little oxycolchicine is injected into a frog, and after a few minutes it is prompted to leap, it performs the act in the usual way and with vigour, but the thighs remain extended and are only slowly drawn up again, and at the same time fibrillary twitchings are evident in the muscles. These phenomena recall the effect of veratrine in the frog. The similarity is the more complete since this drug prolongs the simple muscle-twitch of the isolated nerve-muscle preparation in exactly the same way as veratrine or barium salts. Later the frog shows convulsions, and dies from paralysis of the central nervous system.

Colchicine has a very decided action on leucocytosis. At first, for a period lasting about an hour, it expels the leucocytes from the circulation (hypoleucocytosis). During this period the corpuscles collect in various tissues of the body, especially in the bone-marrow and lungs. The leucocytes soon begin to increase again in the peri-

pheral circulation until there is a very decided augmentation in their number (hyperleucocytosis) (Fig. 20). The alterations in the number of the leucocytes occur almost entirely in the polymorphonuclear variety, the lymphocytes undergoing little or no alteration in number. In consequence, when the circulation contains an excess of these polynuclear corpuscles the bone-marrow shows a diminution in their number. A further effect of this drug is to excite karyokinesis. The exact significance of this action on the marrow cannot be adequately determined at present. It should not be regarded as specific to the leucocytes, but rather a type of the action which goes on to a greater or less degree in other tissues of the body, but is necessarily more easily investigated in the wandering cells of the blood. Small injections of the alkaloid repeated daily increase the number of the basophil cells in the blood without materially altering the total number of leucocytes.

Colchicum is regarded as a specific remedy in cases of acute gout. Gout is a disease in which the tissues form an excess of uric acid, and it was supposed formerly that the benefit of colchicum depended on increased excretion of uric acid by the urine. Colchicum does not increase the excretion of either the uric acid or water of the urine, and so some other hypothesis is necessary to account for its beneficial influence. It is possible that this benefit may be brought about by its action on the connective tissue-cells and white blood-corpuscles, or it may be a nervous effect.

The symptoms of poisoning by colchicum are those of gastro-intestinal irritation—vomiting and purging, and these alone may be responsible for collapse and death. Smaller doses, after a long latent period, produce death by central nervous paralysis.

MATERIA MEDICA

Colchici Cormus.

Dose, 2 to 5 grs.

Preparations

1. **Extractum Colchici.**
   Dose, $\frac{1}{4}$ to 1 gr. (16 to 20 mgrms.).
2. **Vinum Colchici.**
   Dose, 10 to 30 m. (6 to 8 decimils).

Colchici Semina.

Preparation

Tinctura Colchici.

Dose, 5 to 15 m. (3 to 10 decimils).

Colchicine. (Not official.)

Dose, $\frac{1}{100}$ to $\frac{1}{30}$ gr.

DRUGS INCREASING THE EXCRETION OF URIC ACID

For many years attempts have been made to increase the rate of elimination of uric acid in the urine by the internal administration of drugs. These attempts have been for the most part futile; large doses of alkalies, hexamine, and piperazine drugs which dissolve uric acid *in vitro* do not appreciably alter the secretion, whilst salicylates increase both the formation and elimination. The derivatives of quinoline carboxylic acid, however, notably increase the amount of excretion of uric acid, not by increasing its formation, but by facilitating excretion, since after the administration of one of these drugs the percentage amount of uric acid in the blood is definitely diminished. The administration to gouty patients of two or three grams daily diminishes the saturation of the urates in the blood, and hence tends to allow some of the urates in the joints and other parts to pass into solution, and so improvement results. Atophan and other derivatives of quinoline carboxylic acid exert, in other respects, an action very similar to that of quinine. *Atophan* (*Quinophan*, 5-10 decigrms.) 7-15 grs.

THE SEAT OF ACTION

A drug was said formerly to stimulate nerve-endings when its action was eliminated by some other drug which paralysed the nerve without affecting the end-organ. Thus atropine paralyses the vagus and chorda tympani and eliminates the effect of pilocarpine and physostigmine, which stimulate these nerves, but the submaxillary gland and heart are still alive, and therefore pilocarpine, physostigmine, and atropine were all said to act on nerve-endings. Physostigmine causes twitchings in voluntary muscle even after section of the motor-nerve, but the effect is eliminated by curare, which paralyses the motor-nerve without destroying the muscle: both these drugs, then, were therefore said to act on nerve-endings.

Now many drugs, though apparently acting on the "nerve-endings," still exert an action after complete degeneration of the nerve. Physostigmine and perhaps curare lose their effect, and, therefore, may truly be said to act on the nerve-endings. Pilocarpine and adrenalin still act after degeneration of the nerve, and the effect of the former is antagonised by atropine, and the motor effects of the latter by ergotoxin. Hence these drugs must act peripherally to the nerve-endings yet not on the end-cells (muscle or gland), since the effects can be eliminated by atropine or ergotoxin without affecting the end-cells. It becomes necessary, therefore, to introduce a new structure, neither an integral part of the nerve nor end-cell, which we may call for the time the myoneural substance.

Lucas showed the existence of three excitable "things" in

voluntary muscle, one associated with the nerve γ, one with the muscle α, and the most highly excitable, the β, neither associated with the ordinary muscle nor yet with the nerve, but localised in the region of the nerve-ending. Each of these when excited causes contraction (Fig. 21, A). We can extend this conception to plain muscle and obtain an explanation of most of the phenomena with which we have to deal.

Now under normal conditions the nerve impulse must pass from γ to β to α; but drugs may take short cuts and influence either the β or the α directly. Atropine can be regarded as removing the excitability of the β so that the nerve impulse can no longer reach the α. Pilocarpine also affects the β.

Sometimes, however, as in the bladder and intestines, atropine

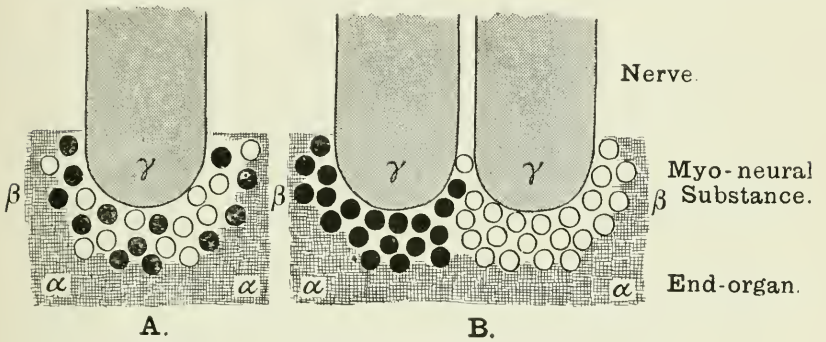


FIG. 21.—SEAT OF PERIPHERAL ACTION OF DRUGS.

α		β		γ	
Barium	+	Pilocarpine	+	Physostigmine	+
Lead	+	Adrenalin	+	Curare	−
Mercury	+	Atropine	−	Cocaine	+
Veratrine	+	Apocodeine	−		
Quinine	+ −	Ergotoxine	−		
Chloroform	−	(motor-nerves only)			
Potash Salts	−				

may still eliminate the pilocarpine action without paralysing the nerve, though it weakens its effect. In this case it is obvious that only a portion of the highly excitable β is paralysed. Supposing that pilocarpine and atropine act upon the clear rings, then after a dose of atropine pilocarpine can no longer produce an effect, though γ can still communicate with the α by the unparalysed portion of the β. If this diagram represents the "nerve-endings" in the uterus we can conceive adrenalin as acting on the β dark circles with undiminished activity, since these are not influenced by atropine, whilst ergotoxin would completely paralyse all the β whilst leaving the α intact, since we know that the contractile substance has lost little or none of its excitability to direct stimulation.

It is quite conceivable, however, that the nerve to the bladder, uterus, and intestine is a mixed nerve, just as we know the sympa-

thetic may be a mixed nerve, in which case the diagram would be more correctly shown in Fig. 21, B. This diagram might also be used to explain the condition in a mixed motor inhibitory sympathetic nerve. Adrenalin in this case causes an explosion in the β, and induces a mixed augmentor inhibitory effect. It is difficult to understand how it comes about that two nerves of essentially the same nature should attract to the neighbourhood of the endings substances of different excitabilities ; or it may be that the reverse is true, and that the highly excitable β determines in some tactic way the position of the ultimate nerve-endings, and in support of this is the fact that the β retains its excitability even in an exaggerated degree months after degenerative section of the nerve.

CHAPTER VI

DRUGS ACTING ON CERTAIN NERVE-CELLS

CONIINE, NICOTINE, LOBELINE, CURARINE, SPARTEINE, GELSEMINE, AND SOME ALLIES OF MORPHINE

General Action

All these drugs have a great similarity in their action: they all induce:—

(1) *Depression and ultimately paralysis of certain nerve-cells.*

(2) *Depression or paralysis of motor nerve-endings.*

(3) *Convulsions which are spinal in origin.*

Blood-pressure and Circulation.—These alkaloids lower blood-pressure, though not to such a great extent as the nitrites; the

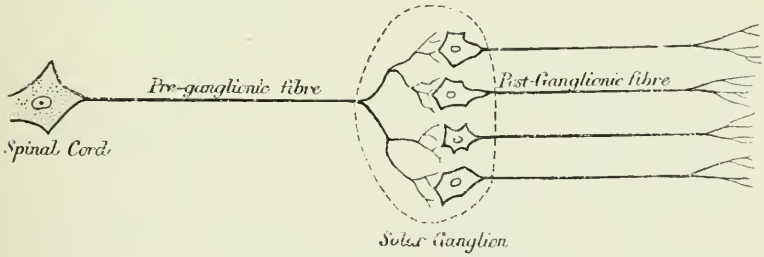


FIG. 22.—DIAGRAM SHOWING THE USUAL ARRANGEMENT OF THE NERVES SUPPLYING THE BLOOD-VESSELS (LANGLEY).

The drugs in this group (coniine, nicotine, &c.) paralyse the nerve-cells in the solar ganglion, and so, by removing tone, dilate the vessels. Hence the pre-ganglionic fibres (splanchnic) on excitation will produce little or no effect, whilst the post-ganglionic fibres will still induce a typical vaso-constriction.

effect is due entirely to vaso-dilatation and is brought about by depression of nerve-cells, especially those on the course of the vaso-constrictor fibres. This can be shown easily by first exciting the splanchnic nerve of an animal and noting the average vaso-constriction of the intestines, and then administering the alkaloid by a vein: excitation of the splanchnic has now no action on the vessels, although if the fibres are excited below the ganglia (post-ganglionic fibres) typical constriction is again obtained (Fig. 22).

The heart beats more rapidly on account of the paralysis of the nerve-cells on the course of the vagus, thereby blocking the inhibitory influences from the centre. The action of nicotine on the

frog's heart will serve as an example: this alkaloid paralyses the vagus, but inhibition of the heart can still be induced by exciting the sinus venosus, *i.e.* the post-ganglionic fibres are intact; this experiment shows again that the block to nerve impulses occurs at the nerve-cells. (Fig. 44.)

Respiration.—The whole brain and medulla are depressed and respiration is therefore slower and shallower.

Plain Muscle.—The tonus and peristaltic movements of the intestines are increased; and not uncommonly purgation may result from the subcutaneous injection of some of the members of this group. This action does not originate peripherally, since the direct application of the drug to the intestines does not augment peristalsis, but rather tends to diminish it; nor is it central in origin, for the drug still increases intestinal movements when the cord is cut in the dorsal region. The effect may be regarded in all cases as due to depression of sympathetic cells, thereby blocking the inhibitory influences. The automatic movements of other plain muscle, such as the stomach and bladder, are increased in the same way.

Effects on some other Nerve-cells.—The nerve-cells on the course of the secretory fibres of the chorda tympani are depressed, so that no secretion of submaxillary saliva is obtained by stimulating the chorda; but the nerve-endings beyond the cells are still active, because a secretion can be obtained either by pressing the electrodes well down into the hilus of the gland, and so reaching the post-ganglionic fibres, or by a small injection of pilocarpine, a drug which specifically excites the nerve-endings.

The superior cervical ganglion of the sympathetic is affected by the members of this group, so that whilst pre-ganglionic excitation is without effect, post-ganglionic excitation produces the usual conditions—constriction of the ear-vessels, dilatation of the pupil, and secretion of saliva. These ganglia may be paralysed either by an injection of the drug into the circulation or by directly painting them with the drug.

Spinal Cord.—Under suitable conditions, all these drugs produce convulsions which closely resemble those obtained by strychnine. There is reason to believe that in each case the effect is due to diminution of resistance on the sensory side of the cord, thereby allowing a simple impulse to spread out and excite motor nerve-cells all over the cord. (*See* p. 119.)

Motor Nerve-endings.—Paralysis of the motor nerve-endings ultimately ensues. Death is produced sometimes by paralysis of the intercostals and phrenics (curarine), and sometimes by paralysis of the medulla (coniine). To observe the motor paralysis with drugs of the latter class the animal must be kept alive by artificial respiration.

Some Differences in Action.—These drugs differ from one another in the relative degree of their actions. Nicotine, coniine, and lobeline are especially characterised by the fact that when they

are injected into the circulation they excite nerve-cells before depressing them; so they give rise first to effects of an opposite kind to those already described, viz. rise in blood-pressure, vasoconstriction, and inhibition of plain muscle; but the real and permanent effects, and the only ones seen when the drug is taken by the mouth, are those which have been described.

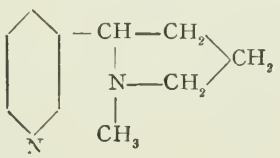
Some bodies of this class do not give rise to convulsions when they are administered in the ordinary way, because the motor paralysis is so rapidly attained. To obtain convulsions with such substances they must be placed either directly on the cord or injected into one of the veins of the cord. A drug of this type is curare. All the members ultimately paralyse the motor nerve-endings; in some cases (curare and methyl-strychnium) with ease, but in others (nicotine) only after comparatively large doses.

The following table gives some idea of the relationship of these drugs to one another.

	Paralysis of Nerve-cells.	Paralysis of Motor Nerve-endings.	Convulsant Effects.
Coniine, Nicotine, Lobeline	Decided. (Initial stimulation when given intravenously.)	Decided.	Weak.
Curare	Weak.	Very decided	Weak (masked by motor paralysis).
Filicic Acid, Kosotoxin	Weak.	Marked.	Marked.
Apocodeine	Marked.	Marked.	Marked.
Apomorphine	Weak.	Weak.	Weak.
Codeine	Still weaker.	Still weaker.	Still weaker.
Morphine	Very weak.	Very weak.	Very weak.
Strychnine	Very weak.	Very weak.	Very decided.

NICOTINE

Nicotine is the volatile alkaloid obtained from tobacco, and is generally represented by the following formula:—



Dried tobacco leaves yield a very variable amount of nicotine, from 2 to 6 per cent. Piturine from *Duboisia Hopwoodii* is pharmacologically identical with nicotine. Nicotine is not used in therapeutics, but since it is of great hygienic importance a few words on its action are necessary.

Tobacco smoke contains several bodies: pyridine bases, hydrocyanic acid, collidine, and several of the higher homologues of nicotine; but it is recognised that the most active constituent of the smoke is nicotine. Cigarette smoke obtained by means of an aspirator gave the following constituents in 100 grams of original tobacco consumed:—

HCN	0.080 per cent.
Pyridine	0.146 „
Nicotine	1.165 „
NH_3	0.360 „
CO	410 c.c.

The smoke contained about 50 per cent. of the nicotine originally in the tobacco; but the quantity depends largely on the length of the mouth-piece.

Nicotine has much the same action as coniine, but has less effect on the motor nerve-endings. Its most important action is on the sympathetic nerve-cells, which at first are excited, later depressed, and ultimately paralysed. This action results in many different effects.

The circulatory system is profoundly influenced by an injection of nicotine. The heart-beat is slowed at first, and later accelerated, and this alteration in rate is the sum of the excitations of the ganglion-cells on the course of the vagus and the sympathetic systems. At first the vagus-ganglia are affected the more profoundly, and the heart is consequently slowed; but as this excitation of vagal cells gives place to depression the stimulation of sympathetic cells shows itself in acceleration of the heart. If the endings of the vagus are first paralysed by atropine, nicotine produces acceleration alone without any initial slowing. Nicotine also excites the vagus-centre in the medulla, as the initial slowing of the heart after an injection of the drug is greater when the vagi are intact than when they are divided. Electrical excitation of the vagi, after large doses of the drug have been administered, fails to inhibit the heart, although muscarine and pilocarpine still slow the beat by stimulating the inhibitory neurone. The ultimate and important effect of nicotine on the pulse-rate is acceleration, and this is due to the blocking of inhibitory impulses.

Nicotine just at first raises arterial tension by an intense excitation of the sympathetic ganglion-cells, particularly those of the solar plexus and allied ganglia. The effect is very transient, and is followed by a fall in the blood-pressure; after big doses of the alkaloid, electrical excitation of the splanchnic nerves produces

no constriction of the intestinal vessels, although post-ganglionic excitation still produces typical constriction, again showing that

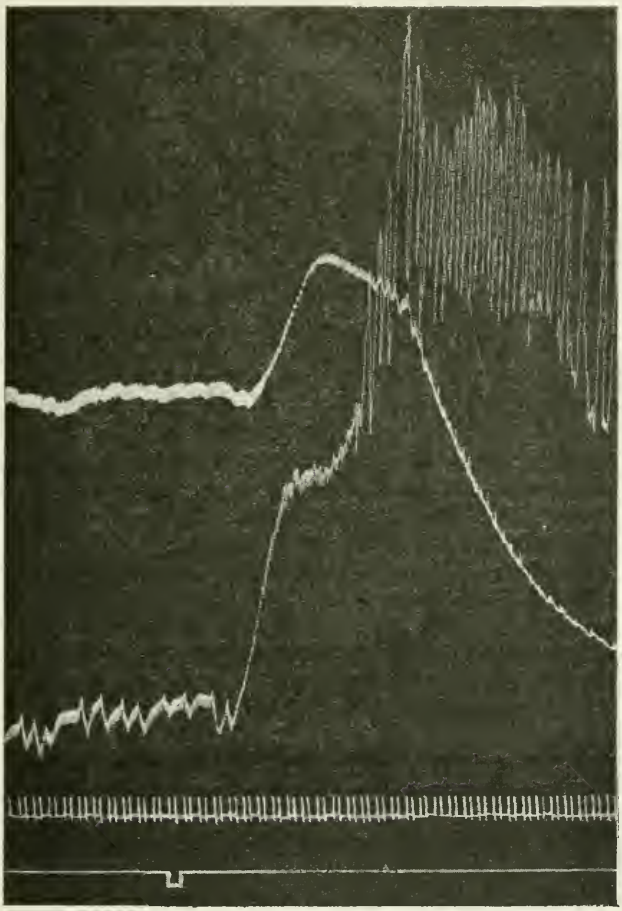


FIG 23.—DOG. LIMB-VOLUME AND BLOOD-PRESSURE.

Upper tracing = limb-volume; lower = B.P. At the indicated mark a small injection of nicotine was given. The B.P. rose immediately, and the heart became very slow. The latter effect is the result of the high pressure on the medulla, for if the vagi be severed the heart will at once beat very much more rapidly. Vaso-constriction is responsible for the rise in pressure. Constriction of the limb-vessels is shown both by the position of the curve and the diminution of the volume-pulse. The first vessels to constrict are the splanchnic; and so, just at first, the increased blood-pressure causes the limb-vessels to dilate. Time = secs.

the block is in the ganglion-cells. The ultimate effect on the circulation is vaso-dilatation, a fall of blood-pressure, and acccleration of the heart.

The movements of plain muscle throughout the body are first inhibited and later augmented, these effects being due to the initial excitation and ultimate paralysis of sympathetic nerve-cells.

The effect on the pupil varies considerably in different animals, and should be regarded as the mean effect on the ciliary and sympathetic-ganglion cells.

Many of the secretions are at first increased by nicotine, the seat of action being the ganglion-cells on the secretory nerves. In the case of the submaxillary gland, which has been most fully investigated, small doses of nicotine increase the secretion; but large doses stop all secretion, and in this case excitation of the chorda tympani, which in the normal animal produces a large flow of saliva, now gives no result. If, however, the nerve-fibres are stimulated between the ganglion-cells and the gland-cells a secretion is obtained. Pilocarpine still produces a flow of saliva after the injection of a big dose of nicotine, because it acts on the nerve-terminations in the gland-cells. The sweat and bronchial mucus are increased similarly by small injections of nicotine (Fig. 11).

Motor Nerve-endings are affected only with difficulty; very large quantities of nicotine paralyse these nerve-endings, and, like curare, those supplying the orbital muscles are affected first.

The effect on the **Central Nervous System** in all cases is shown by increased reflexes and sometimes by strychnine-like convulsions. This effect is peculiar to all the members of the group, and although it results in stimulation—that is, increased reflexes—we cannot say whether it is brought about by excitation or depression of the sensory part of the cord. The initial excitation of cells, which is peculiar to nicotine, is shown in the deep and rapid respiration seen for a very short time after exhibiting the alkaloid internally: this action is quickly followed by depression, which is the characteristic effect of all the members of the group.

The initial stimulant effect of nicotine can be seen also if a 0.1 per cent. solution is applied directly to the spinal cord of a frog, when twitchings of the muscles of the limbs, sternum, and other parts are observed. They are irregular in character, are not reflex, and in no way resemble the clonic convulsions of strychnine: the action is apparently one on the motor nerve-cells, which explode without receiving an afferent impulse.

The animal body rapidly acquires a tolerance to nicotine. It is well known that the common symptoms of a first attempt at smoking —vomiting, depression, and collapse—are quickly overcome by a few trials. Nicotine is mainly excreted by the kidneys: traces are to be found also in the saliva and sweat.

The administration of a toxic dose of nicotine produces a feeling of burning in the mouth, throat, and stomach, accompanied by salivation and later by vomiting and diarrhœa. The patient at first is much excited and both his respiration and pulse are accelerated; but soon the excitement is followed by languor, loss of co-ordination, exhaustion, and later by loss of consciousness.

Tobacco.—Nicotine itself rarely gives rise to poisoning, but excessive smoking not infrequently induces objectionable effects.

Before describing these it should be noted that the pyridine bodies present in tobacco smoke have an action different from nicotine: they excite the medulla and cord more readily, and so may produce general convulsions. The products of the dry distillation of almost any leaves will induce nausea, vomiting, diarrhœa, and palpitation from the presence of such pyridine-compounds.

Chronic intoxication, the result of smoking to excess, may induce the following symptoms:—Cough due to congestion of the air passages, alimentary disorders such as loss of appetite, vomiting, and diarrhœa; a feeble and intermittent action of the heart is a very common feature of poisoning. In more severe cases depression of the central nervous system, tremors, impaired memory, and amblyopia may ensue. The amblyopia affects both eyes equally, and begins with a general dimness of vision and a change in colour-perception; it is a nervous affection, thought by some to be localised in the nervous layer of the retina, and by others in the centre.

It is not uncommon to find 2 or 3 per cent. of CO in the blood of cigarette smokers.

CONIUM

Conium leaves are obtained from the spotted hemlock, *Conium maculatum*. They are mistaken sometimes for fool's parsley, *Æthusa cynapium*, but conium has certain distinctive characteristics —a smooth, spotted, hollow stem, much divided glabrous leaves, with their ultimate divisions terminating in smooth, colourless points and the presence of both partial and general involucres.

The chief constituents of hemlock leaves are about 2 per cent. of the alkaloids coniine and conhydrine. The most characteristic effect of coniine is a general diminution of motor power (paralysis), as is seen in the wearied, unsteady gait, followed by reeling and marked ataxia; the excitability of the motor nerves is ultimately abolished. The breathing becomes slower and weaker, and death occurs from its arrest. It is uncertain whether death is due to paralysis of the motor nerve-endings or to paralysis of the medulla, but it is certain that the medulla is paralysed before the motor nerves cease to respond to electricity.

LOBELIA

Lobelia is the dried flowering herb *Lobelia inflata;* it is also known as Indian tobacco. Its chief constituent is the liquid alkaloid lobeline, which forms crystalline salts.

In its general action the drug appears to resemble coniine and nicotine, and death is produced by paralysis of the respiratory centre. It is employed in certain spasmodic conditions as an antispasmodic and expectorant, especially in constriction of the bronchioles (asthma). It is well known that if the vagi are stimulated the calibre of the air passages is decreased; air can still enter

the air-cells, but it has great difficulty in escaping, because inspiration is a very powerful suction, but expiration depends mainly on the elastic recoil of the lungs, a comparatively feeble force ; so that the lungs become over-distended. Lobelia depresses the peripheral vagus just like coniine, and after its administration the bronchioles cannot be constricted by vagal stimulation. If an attack of "asthma" is induced artificially by the administration of a drug, such as pilocarpine, lobelia produces a quick dilatation which is not lasting unless the dose has been large (Fig. 24).

GELSEMIUM

Gelsemium is the root from the yellow jasmine, *G. nitidum*. The chief constituent is the alkaloid gelseminine, which forms amorphous

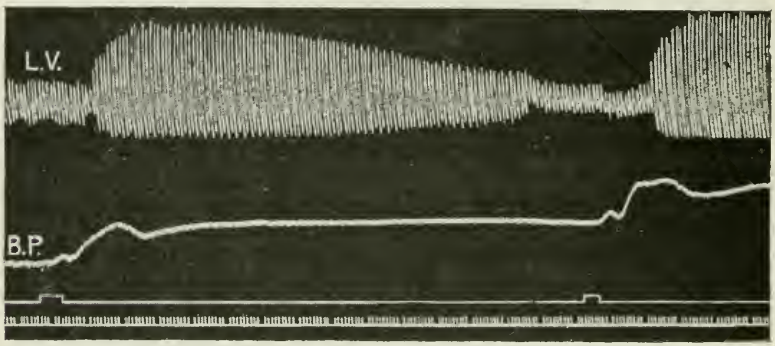


FIG. 24.—CAT. LUNG-VOLUME AND BLOOD-PRESSURE.

Upper curve represents the volume of a small lobe of lung; lower curve represents blood-pressure. The amount of air entering and leaving the lungs is shown by the up and down strokes respectively. At the two indicated marks, small doses of tincture of lobelia were injected into a vein. Almost immediately, more air entered the lungs because the bronchioles dilate. The first effect was transitory, because the dose was small. The rise in B.P. is vaso-motor. Time = secs. (Brodie and Dixon.)

salts. A second alkaloid, gelsemine, is crystalline. Other constituents are gelsemic acid, a crystalline substance exhibiting in alkaline solutions a blue-green fluorescence, a volatile oil, resin and starch.

The action of the drug depends on the gelseminine, which has much the same effect as coniine, but is more depressant to the central nervous system, and produces death by paralysing the respiratory centre rather than by paralysing the nerve-endings in the diaphragm and intercostals. If coniine is injected into a frog the motor nerve-endings are paralysed first and the centre later ; gelseminine, however, paralyses the centre first and the nerve-endings afterwards.

Gelseminine paralyses nerve-cells without any preliminary excitation, and hence the vagi are paralysed. The injection of gelseminine does not affect the pupil, but if a salt of the alkaloid is applied to the conjunctiva there is some slight pain followed by

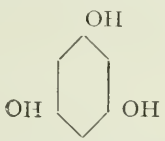
dilatation of the pupil and paralysis of accommodation. This effect is produced apparently in the same way as that of atropine, by paralysis of the endings of the third nerve; it differs from atropine in that it does not persist so long and is less complete. Large doses of gelseminine first produce loss of power, inco-ordination of movements, and tremors. The pulse is quicker; the respiration becomes progressively slower and feebler till death ensues from asphyxia.

Consciousness is retained to the end.

Gelsemine is very much less toxic than gelseminine, but in large doses it produces convulsions in frogs in the same way as strychnine, and later paralyses the motor nerve-endings. It is almost devoid of action in mammals.

SCOPARIUM

Broom-tops are obtained from *Cytisus scoparius*. The chief constituent is the liquid volatile alkaloid sparteine, $C_{15}H_{26}N_2$, which forms crystalline salts. The drug also contains a body, scoparin, which forms yellow crystals and contains the phloroglucinol complex.



Other constituents are a volatile oil and tannin. Sparteine has an action very similar to coniine, but is very much less poisonous. It differs from coniine in that it has very little effect on the central nervous system, but large doses paralyse sympathetic nerve-cells and the peripheral terminations of the motor nerves. There is hardly any excitation of the nerve-cells, so that although blood-pressure at first rises a very little, it quickly falls. Death is brought about by paralysis of the nerve-endings of the phrenics.

At one time sparteine was believed to be related pharmacologically to digitalis, but there is no similarity in the actions of the two drugs.

Decoction of broom-tops is used as a diuretic, but it has very little action (*see* Diuretics).

CURARE

Curare is a resinous material employed by the South American Indians as an arrow-poison and obtained from some plant of the Strychnos group. The active constituents are (1) curarine, $C_{18}H_{35}N$, the substance to which the curare owes its typical effect, and (2) curine, $C_{18}H_{19}NO_3$, which has certain digitalis-like properties.

Absorption.—One of the most remarkable features of curare is that its effects are only obtained when the drug is introduced into the body subcutaneously or intravenously. Fish, for example, live for days in a solution, but die very quickly if a slight scratch is made on their skin. If the drug is taken by the mouth, generally speaking, it produces no effect, although after very large doses slow poisoning may sometimes ensue. The cause of this is probably twofold. In the first place, when curare is digested with gastric juice its toxicity is diminished; and, secondly, the curarine appears

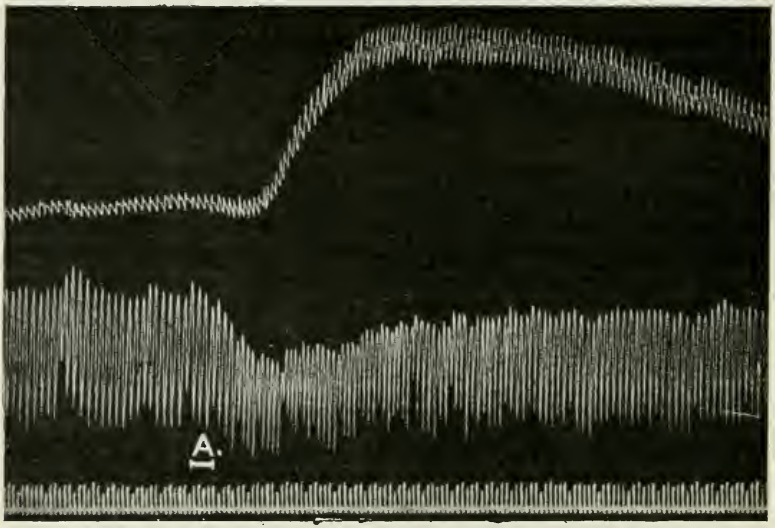


FIG. 25.—DOG. A.C.E. LIMB-VOLUME AND BLOOD-PRESSURE.

Shows the effect of an injection of curare at A into a vein. The ganglion-cells on the course of the vaso-constrictor nerves are depressed and vaso-dilatation ensues with a fall of B.P. The dilatation is shown (1) by the rise in the upper curve, and (2) by its greater volume-pulse. The heart-beat is quicker, principally on account of the depression of the cells on the vagus nerves. Time = secs.

to be more rapidly excreted than it is absorbed; the latter fact may be shown by administering the curare by the mouth after the renal vessels have been ligatured, when poisoning is quickly produced.

Nerve-endings.—The effect of curare on the motor nerve-endings overshadows all its other effects. The short muscles of the fingers, toes, ears, and eyes are affected first, then the muscles of the limbs, head, and neck, and, lastly, the respiration. The first effect of the drug is to produce a condition similar to that caused by fatigue, then the strength of contraction is diminished, and, lastly, excitation of the nerve elicits no response, although a normal contraction is produced if the muscle is stimulated directly.

The paralysis does not affect the sensory nerves; this was shown by Claude Bernard. He ligatured the whole of one hind-limb of a frog with the exception of the sciatic nerve, which remained intact

outside the ligature: he then injected the curare, and when the animal was immobile pinched the skin of one fore-limb, when there was a reflex movement of the ligatured hind-limb, thus showing that the sensory endings of the fore-leg must be intact as well as the nervous arc (cells of spinal cord). Kühne first produced clear evidence which showed that no such simple interpretation of the motor paralysis was possible. He worked with the sartorius muscle of the frog and showed that the irritability of the different parts of this muscle varied with the number of nerve-endings: it was most irritable at the point of entrance of the nerve and least at the ends where nerve-endings were absent. He then showed that a paralysing dose of curare did not abolish this difference in irritability. Therefore, either curare does not act upon the nerve-endings, or if it does the varying irritability of the muscle must be due to inherent differences in the muscle-cells. Kühne decided against the latter view, because he found that if he passed a constant current through the nerve to the muscle, with the positive pole near the muscle so that the end of the nerve was thrown into electrotonus, the irritability of the muscle became the same throughout. He felt then compelled to conclude that curare did not act upon the nerve-terminals, although after the administration of very large doses he admits that the whole nerve-ending might be paralysed.

Sympathetic ganglia are not much affected, though sufficiently so to show an increase of peristalsis. Convulsions are seen only when the drug is injected directly into the vessels of the cord. In the ordinary course of events the motor paralysis hides this effect.

Curare sometimes gives rise to sugar in the urine, and although this may be due in part to a deficient or too plentiful artificial respiration, there is sufficient evidence to show that it is due in part to the direct action of the drug.

MATERIA MEDICA

LOBELIA

Lobelia.

PREPARATION

Tinctura Lobeliæ Etherea.

Dose, 5 to 15 m. (3 to 10 decimils).

GELSEMIUM

Gelsemii Radix.

Dose, of gelsemine hydrochloride, $\frac{1}{60}$ to $\frac{1}{20}$ **gr.**

PREPARATION

Tinctura Gelsemii.

Dose, 5 to 15 m. (3 to 10 decimils).

BROOM

Scoparii Cacumina.

Preparations

1. **Infusum Scoparii.**
   Dose, 1 to 2 oz. (30 to 60 mils).
2. **Succus Scoparii.**
   Dose, 1 to 2 drs. (4 to 8 mils).

CURARE

Curara. (Not official.)
Dose, $\frac{1}{20}$ **to** $\frac{1}{2}$ **gr. subcutaneously.**

TOBACCO

Tabaci Folia. (Not official.)

CHAPTER VII

DRUGS WHICH PRODUCE CONVULSIONS

Drugs affect the nervous system in one of two ways, stimulation or depression. By a drug which stimulates we mean one which exaggerates the normal response of a tissue to excitation; and a drug which stimulates the spinal cord, therefore, increases the reflex movements, and may, if they are sufficiently exaggerated, produce convulsions. It has been pointed out already in the chapter on alcohol that this stimulation can be produced in two ways: (1) by direct excitation; and (2) by depression of controlling centres.

All convulsive poisons in sufficiently large doses have a paralysing action. Strychnine, ammonium salts, veratrine, and other convulsants in very large doses ultimately produce depression and paralysis of the central nervous system provided the animals do not die during the convulsions; and sometimes, as in the case of strychnine, there is paralysis of the motor nerve-endings. Some authorities have attempted to show that the reverse law holds true, that all drugs producing depression have an initial stimulating effect, and cite alcohol and chloroform as examples; but the student will understand how fallacious such reasoning is, for both these drugs probably depress from the beginning. (*See* p. 43.)

After the administration of a convulsant there is a short period of increased reflex excitability, and then sudden tonic contractions of all the muscles in the body lasting some seconds, followed by a complete relaxation. After a variable interval the convulsions recur until the death or recovery of the animal. The attacks present many similarities to the ordinary epileptic fit. Death occurs from asphyxia, and is all the quicker because of the rapid consumption of oxygen during the convulsions. If an adequate artificial respiration is exercised the dose of a convulsant can be increased to an enormous extent without producing death; not only does it prevent death from asphyxia, but it also diminishes the reflex sensibility of the medulla.

Different drugs exert a specific action on special neurones or on parts of the neurone. Thus atropine attacks the nerve-endings of the third and tenth cranial nerves, curare motor nerve-endings, coniine sympathetic nerve-cells, caffeine the psychical centres in the brain, and so on. And as the great difference between man and the

lower animals consists in the greater development of his central nervous system, so we should *a priori* expect drugs which act on the neurones of the brain to exert differences in action according to the development of that organ. This we find to be the case. Atropine, which produces some convulsive movements in man, produces none in other animals, because its action is on the motor area, which is much more highly specialised in man than in lower animals. Cocaine produces convulsions which vary in extent in different animals according to the degree of development of the cerebral hemispheres. They can be produced by very small doses in man, somewhat larger amounts in the ape, still larger in the dog, only with relatively enormous doses in the rabbit, and cannot be produced at all in the frog. In the following diagram of the central nervous system the seat of action of a number of drugs is shown, but it must be remembered that although the action is particularly on the tissue indicated, yet a drug which excites one part of the central nervous system invariably excites all parts, although its action is more pronounced on the one part (Fig. 26).

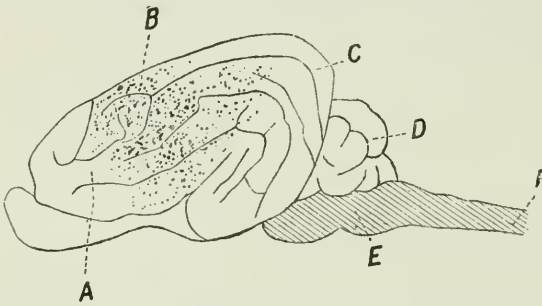


FIG. 26.—DIAGRAMMATIC VIEW OF A DOG'S BRAIN.
Showing the various points which drugs may excite, and so produce convulsions or convulsive movements. (See text.)

A. Drugs acting on highest or psychical centres:—Caffeine and other purine derivatives.

B. Drugs acting on the motor area:—Atropine, cocaine, essential oils, santonin.

C. Drugs acting on the posterior portion of the cerebrum:—Mescal.

D. Drugs acting on the cerebellum:—Not known for certain.

E. Drugs acting on the medulla:—Strychnine, "ammonium," picrotoxin.

F. Drugs acting on the cord:—Strychnine, calabarine, filicic acid, kosotoxin.

NUX VOMICA

Nux vomica is the name of the dried seeds of *Strychnos nux vomica*. They contain two alkaloids, strychnine and brucine, present in any amount up to 5 per cent. The relative amount of strychnine to brucine is extremely variable; either may be present in double the amount of the other. Since brucine is much less poisonous than strychnine (about $\frac{1}{30}$), it is officially directed that the

proportion of strychnine shall be determined in the preparations. A glucoside, loganin, and some tannin are also present in the beans. Strychnine exerts the same action as the crude preparations of nux vomica, but its effects are produced more quickly and with more certainty.

Action

(1) *Bitter effect on the alimentary canal.*
(2) *An effect on the sensory part of the cord resulting in increase of reflexes, increased tonus and work of muscle, followed by reaction.*
(3) *Stimulation of the circulation and respiration.*
(4) *Heightened perception from all the sense-organs.*

Gastro-intestinal.—Strychnine has a bitter action in the mouth, and, as we shall see when studying the simple bitters—a class of bodies that owe their action to their bitterness—it therefore increases the appetite, and as a result the gastric juice is augmented reflexly.

Like almost all other drugs, it is absorbed only very slightly from the stomach. The relative rate of absorption from different parts of the alimentary canal has been determined by injecting a big dose of the alkaloid into various portions of the isolated gut, and then noting the time between the injection and the onset of convulsions. By such experiments the following table was drawn out:—

About 1½ grs. strychnine injected into the stomach of a cat produced tetanus in thirty minutes.
About 1½ grs. strychnine injected into the small intestine produced tetanus in ten minutes.
About 1½ grs. strychnine injected into the œsophagus produced tetanus in fifty minutes.
About 1½ grs. strychnine injected into the colon produced tetanus in fourteen minutes.
About 1½ grs. strychnine injected into the rectum produced tetanus in seven minutes.

This table gives roughly an idea of the relative rate of absorption by the alimentary canal of most of the non-volatile alkaloids. Having reached the blood-stream, strychnine exerts its specific action on the central nervous system, and it will be convenient to consider its action on the cord, medulla, and cerebrum separately.

Cord.—If a poisonous dose of strychnine is administered to an animal or to man, for the action is the same in all vertebrates, the reflexes are quickly heightened, so that such a stimulation as a slight noise leads to an exaggerated start. There is a certain restlessness with occasionally involuntary twitchings of muscles, and then without further warning a convulsion occurs, affecting all the muscles of the body. The extensor muscles being more powerful than the flexor, they overshadow the effect of the latter so that the animal's head is thrown back, the fore and hind limbs are extended, and the

trunk forms an arch with its concavity backwards ; this condition is termed opisthotonus. In a variable period, generally between ten and sixty seconds, relaxation occurs ; this is not uniform, so that the *tonic* state is succeeded by irregular *clonic* contractions before relaxation is complete.

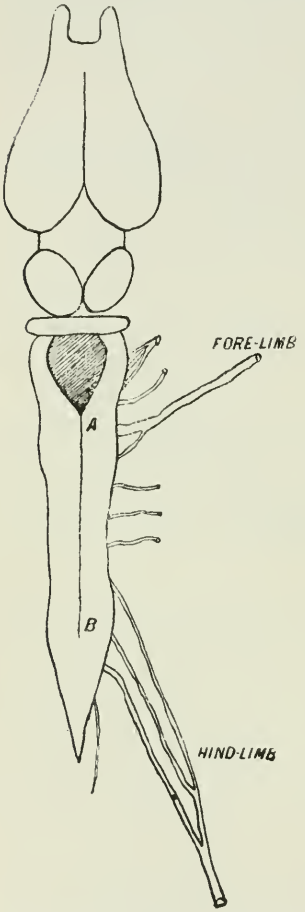


FIG. 27.—DORSAL SURFACE OF THE CENTRAL NERVOUS SYSTEM OF A FROG.

If the cord is exposed, and a little strychnine is painted on it in the region A, general convulsions ensue on pinching one fore-limb. But the motor cells at B must be intact, for pinching the hind-limb produces a normal reflex. Therefore, convulsions may occur when the motor cells are normal.

This action of strychnine is not on the brain, for convulsions are still produced in the decapitated frog. Neither is it on the motor nerve-endings nor muscle, because section of the nerve stops the spasms. The convulsions would seem therefore to have their origin in the cord, and we find that as the cord of a strychninised frog is destroyed from above downwards, so the convulsions cease in the same order. The convulsions are not initiated in the cord, but from a definite stimulus, which is generally from the surface of the body. If a frog, which has had all its sensory nerve-roots cut across, is given a moderate injection of strychnine, tetanus does not ensue ; or if the animal is bathed in a 5 per cent. solution of cocaine, an alkaloid which paralyses some portion of the peripheral sensory apparatus, quite a big dose of strychnine produces no convulsions. The convulsions, therefore, arise only after an appropriate stimulus. The sensory cells on the posterior horns do not influence the condition, for typical convulsions are still to be obtained after the posterior root-ganglia are all severed, by exciting their central cut-ends.

Having then clearly shown that strychnine acts on the cord, and that this effect consists in the nature of an exaggerated reflex initiated by some external stimulus, we may consider the portion of the cord on which it acts. When a small stimulus is applied to a normal animal it responds in a definite way by a few of its muscles contracting ; but under the influence of strychnine the impulse spreads out, with the result that every motor cell in the cord explodes. There is reason to believe that this effect is not on the

motor cells directly. If a frog is decapitated posterior to the cerebral hemispheres and eviscerated, and if its cord is exposed over the brachial plexus and a little strychnine placed on it (at A in Fig. 27), in a few minutes typical convulsions over the whole body can be obtained by pinching one of the fore-limbs. That is to say, convulsions are obtained in the hind-limbs as well as the fore-

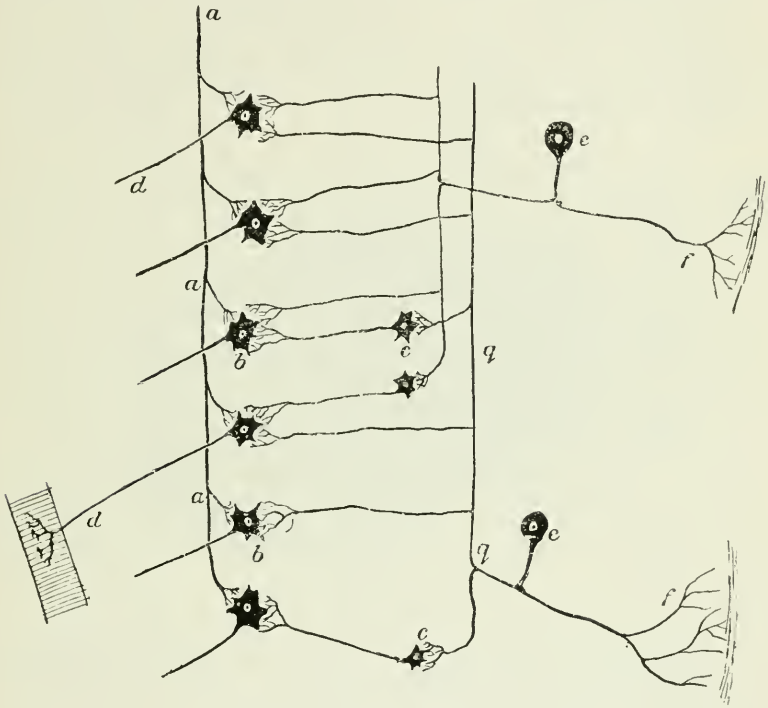


FIG. 28.—DIAGRAM SHOWING NERVE-CONNEXIONS IN THE SPINAL CORD.

a = fibre of the pyramidal tract; *b* = motor cells in anterior cornu; *c* = sensory cells; *d* = motor nerves going to muscle; *e* = posterior root ganglia; *f* = sensory nerve-endings in skin; *q* = sensory fibres.

Strychnine acts on some portion of the sensory apparatus *q*—probably either the cells *c* or the sensory arborisations round cells—in such a way that a normal impulse beginning at *f*, instead of confining its direction to one path of least resistance and terminating at *d*, now spreads out and affects all motor cells.

limbs, although the nerve-cells supplying the former (those at B) are not affected by strychnine. Further, if the hind-limb is pinched the leg contracts in a normal manner, showing that these motor cells are intact. Hence the action must be on some part of the sensory side of the cord, and a limited number of strychninised sensory cells can throw every motor cell in the body into activity. Motor neurones, on the contrary, cannot transmit independently exciting stimuli to each other. We must regard the sensory cell as imposing under normal conditions a resistance to the passage

of an impulse and so directing its course into a definite channel. This directing action and resistance is destroyed by strychnine, all paths become equally easy, so that a single afferent impulse may spread to all the motor cells. Now it has been shown by Sherrington that reflex excitation of a flexor muscle is associated with inhibition of its antagonist (extensor), so that both cannot be excited to contract at the same time. A reciprocal innervation exists between the motor cells for these antagonistic muscles. Small doses of strychnine cause a diminution of this inhibitory effect, and large doses may even replace it by contraction, so that flexor and extensor muscles may contract at the same time. Such a condition occurs

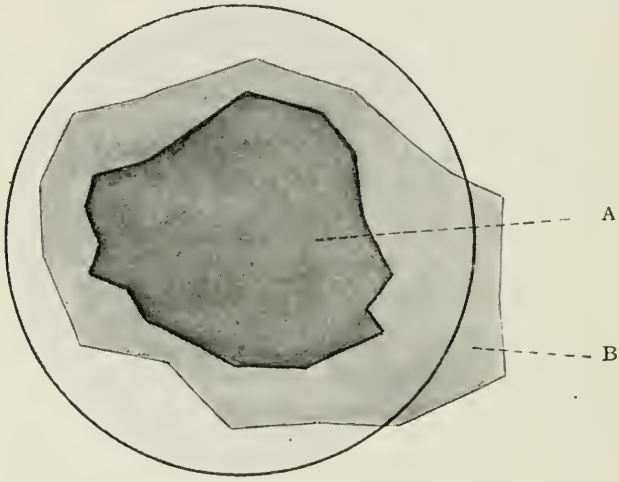


FIG. 29.

A is a diagram of the field of vision of a healthy man as measured by the perimeter. B is another estimation fifteen minutes after the injection of $\frac{1}{50}$ grain of strychnine. This chart was mapped out for the perception of blue, the field of vision for which is especially increased by strychnine.

in opisthotonus. This effect may be interpreted by supposing that strychnine diminishes the resistance of afferent impulses and renders all paths equally easy. A skin stimulation, instead of passing in the direction of least resistance through A and B (Fig. 30) and causing contraction of the flexor and relaxation of the extensor under the influence of strychnine, also passes through C, and this motor effect overshadows the inhibitory impulse through B.

Three minims of Liquor strych. hydroch. at first increases *muscular work* as measured by the ergograph ; the effect is gradually produced and reaches its maximum in three hours. Seven minims has the same action, but the maximum effect is reached in half an hour. In both cases the work rapidly falls off after the maximum is reached ; that is, the initial increase of work is followed by a secondary diminution. The spinal cord is the seat of action.

The **medulla** is affected in the same way as the cord, the ordinary afferent stimuli producing exaggerated effects. The respiratory movements depend on afferent impulses reaching the medulla, and strychnine increases and exaggerates these so that the movements of respiration are both quicker and deeper; hence the alkaloid may be valuable in bronchitis and allied conditions in which the centre is much depressed, and cough in consequence very feeble. In poisonous doses death occurs from asphyxia by fixation of the respiratory muscles during the convulsions.

The vaso-motor centre is stimulated and the peripheral vessels constrict. The vagal centre is also excited so that the heart-beat is slower than normal.

On the **cerebrum** strychnine produces comparatively little effect. The motor area is said to be slightly more irritable to direct electrical stimulation than in the normal state, but the higher centres are influenced very little. The intellect remains unclouded till death, and symptoms such as giddiness or ataxia, suggesting an action on the brain, are absent.

Sense-Organs.—Careful observation has revealed that strychnine has a decided action on the sense-organs.

The sense of smell is more acute and is said to be altered so that a pleasant odour becomes more agreeable, and an unpleasant odour less disagreeable. The effect lasts for about twenty-four hours. The sense of touch is more delicate. The points of a pair of dividers when applied to the skin may be recognised as two points, which felt like one point previous to taking the strychnine. Hearing is certainly more acute, for the tick of a watch is appreciated farther off than normally. The acuity of vision is increased; differences in shades of colour become visible which were not appreciated by the normal vision, and the field of vision, especially for blue colours, is enlarged. These effects are due to the action of strychnine on some part of the sensory nervous apparatus, but whether peripheral, as, for example, in the

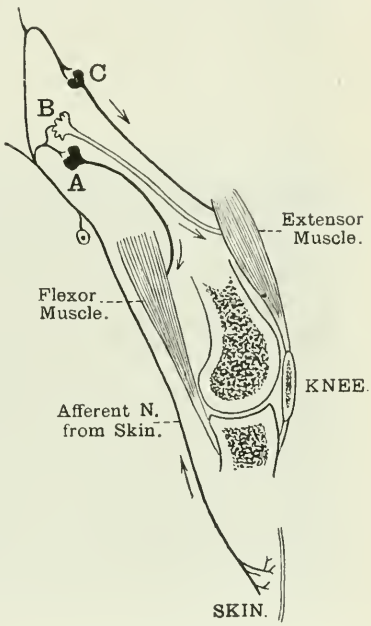


FIG. 30.—DIAGRAM SHOWING THE RECIPROCAL INNERVATION OF TWO KNEE MUSCLES.

A skin stimulation below the knee causes contraction of the flexor muscles through the cells A, and inhibition of the extensor through the cells B. Strychnine eliminates resistance: under this drug impulses from the skin also pass through C, which represent the motor cells to the extensor muscles. By this means flexors and extensors may contract simultaneously.

retina, or central in the brain, we must for the present leave undecided.

Heart and Vessels.—The action on the circulation, though not very great, is said to be of practical importance. The strength of the beat in the isolated heart of the frog and mammal is increased, though not to any great extent, by small doses of strychnine. This is due, probably, to an action directly on cardiac muscle. Blood-pressure is raised mainly on account of vaso-constriction due to stimulation of the medulla, so that strychnine in some cases improves the pulse, and is largely and properly employed in cases of cardiac failure as a tonic to the circulatory system. But some of this vaso-constriction is no doubt peripheral in origin,

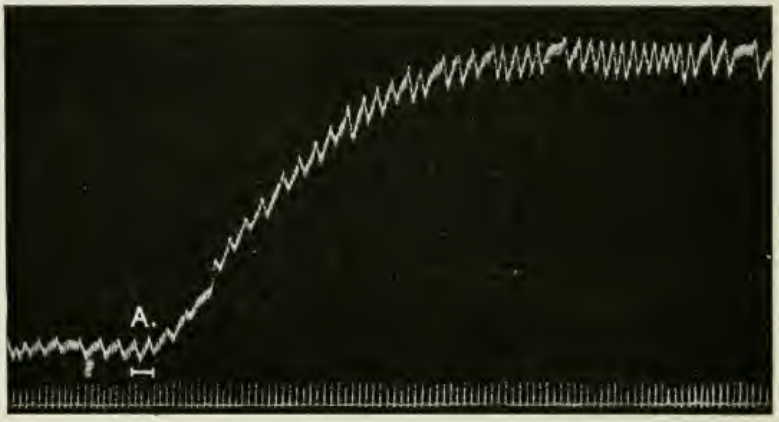


FIG. 31.—DOG. A.C.E. CURARE. BLOOD-PRESSURE.

At A $\frac{1}{10}$ grain strychnine was injected into a vein. The effect is due to vaso-constriction, both the centre in the medulla and the nerve-endings in the vessels being excited. As the motor nerve-endings are paralysed, artificial respiration is being carried on. The action of strychnine on the circulation is, however, quite insignificant when compared with that of digitalis.

because when strychnine is perfused through the vessels of an isolated organ a diminished outflow from the vein is obtained. The rise in blood-pressure can equally well be obtained after curare, and such a rise after an intravenous injection of strychnine is shown in Fig. 31. This rise must not be confounded with the very large and temporary rises seen in Fig. 32, and due to the intense contraction of the voluntary muscles resulting from the convulsions. The action on the centre slows the rate of the heart slightly.

The skin-vessels are dilated, not constricted. It is not exceptional, as we have already seen under atropine, to find a drug which, like strychnine, acts centrally and induces vaso-constriction of the splanchnic vessels and, at the same time, dilatation of the skin-vessels.

Other Effects.—Strychnine by augmenting all the reflexes of the cord increases those pertaining to the reproductive organs, and

in the male is employed as aphrodisiac and in the female as an emmenagogue.

All convulsants by increasing the movements of the body tend to raise the temperature and augment metabolism. The rise in *temperature* is counterbalanced by the dilatation of the skin-vessels, so that in most large animals the temperature does not rise, and not infrequently it falls. The increased movements are also responsible for an enlarged consumption of oxygen and a greater carbonic-acid output, as well as for an increased destruction of the glycogen of the liver. During the convulsions the internal absorption of

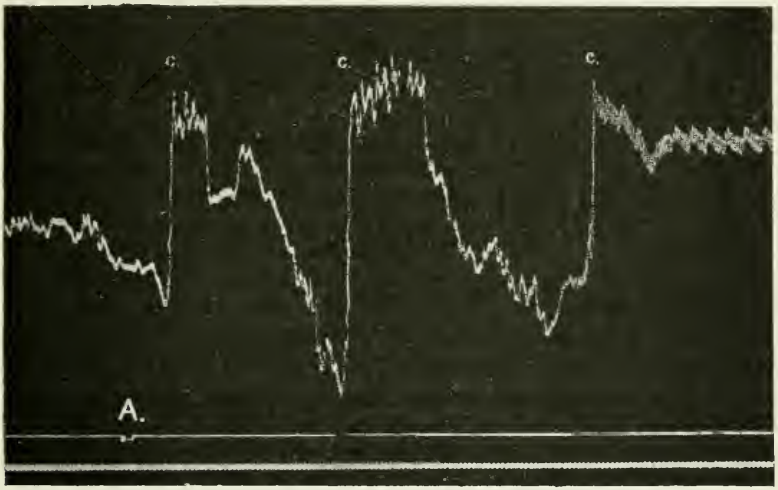


FIG. 32.—CAT (DECEREBRATE). BLOOD-PRESSURE.

At A $\frac{1}{10}$ grain strychnine HCl was injected into a vein. The three separate increases of pressure at the C are due to convulsions. Time = secs.

oxygen is enormous, and as the chest is immovable, asphyxia is extremely rapid.

Strychnine increases the tonus of *plain muscle* throughout the body just as in the case of striped muscle, and like the latter effect it is probably due to exaggerated nervous reflexes. Thus Auerbach's plexus is said to be stimulated just as it is by small doses of atropine, so that afferent impulses produce larger peristaltic effects. It is, therefore, employed in such conditions as chronic constipation, atony of the bladder, or in any other condition where an increase of tone in plain muscle is desirable. This action is never pronounced.

Strychnine, like most alkaloids, is *excreted* in the urine. The excretion is slow, for traces of the alkaloid may often be found in the urine four or five days after the administration has ceased. Possibly a small portion is oxidised in the body, but there is no evidence that

this power of oxidation can be cultivated and a tolerance produced to the drug.

The **symptoms** of poisoning (after about ½ gr.) come on quickly five or ten minutes after administration.

There is first a stage of excitement in which the patient is very restless, his special senses are all sharpened, and tremors and involuntary twitchings of scattered muscles are apt to occur. But in a moment the whole body becomes stiff and rigid, all the muscles are tense : this is opisthotonus. In this condition respiration ceases and rapid cyanosis comes on. The angles of the patient's mouth are drawn down and give rise to the condition known as "risus sardonicus." Consciousness remains perfect to the end and the patient suffers acute pain, both mental and physical.

In a minute or two muscular tension relaxes. The relaxation is not uniform, so that the tonic stage is succeeded by a clonic in which violent and irregular contractions of the muscles occur ; this gradually subsides, the cyanosis goes, and the patient lies exhausted and bathed in perspiration. This attack is soon followed by another, and death occurs either in a paroxysm from asphyxia or, in the intervals, from exhaustion. In the disease known as tetanus the symptoms begin with pain and stiffness of the neck and jaws, and the tetanic symptoms come on much more slowly. In strychnine poisoning the symptoms begin acutely, a general convulsion at once seizes the whole body, and the relaxation is complete ; but in tetanus there is some permanent muscular rigidity.

Treatment in the first place must be aimed at getting rid of any strychnine still present in the stomach. If convulsions are present the use of the stomach-pump is impossible, but emetics, such as mustard or ammonium carbonate, should be administered. Potassium permanganate or tannin can be employed as chemical antidotes to render the strychnine inactive. But it is more often necessary to do something to relieve the convulsions. For this purpose the narcotics may be exhibited ; the convulsions can be controlled by anæsthesia, and large doses of chloral, bromides, alcohol, or urethane are all useful. Urethane is particularly valuable, for strychnine has no power to produce convulsions in an animal under the influence of this drug. The fatal dose of strychnine varies from ½ to 1½ grs.

If strychnine combines chemically with some portion of the spinal cord, it would seem probable that an emulsion of the alkaloid and spinal cord should be inactive. Such an emulsion, containing twice the minimal lethal dose of strychnine, when injected into an animal subcutaneously, is still poisonous, though, perhaps, a little less toxic than normally. This experiment, however, proves nothing, as if the strychnine is injected along with any lipoid its toxicity is reduced as the result of delayed absorption. No evidence, therefore, exists that it enters into a loose combination with a

substance in the cells of the cord. All the evidence points in the other direction.

Other drugs which give rise to symptoms like those of strychnine are :—*Brucine*, which is dimethoxy-strychnine, is less toxic but more bitter than strychnine : it causes, also, a different type of convulsions ; *Calabarine*, present in minute quantity in the Calabar bean, and of little practical significance ; certain of the *opium alkaloids*.

All this last group, including morphine, have a tendency under certain conditions to produce the most marked "strychnine-convulsions." The convulsant action of narcotine is, however, more important practically than that of the others, as it is present sometimes in large quantities in certain opiums, and is partly responsible for the increased reflexes which are seen after an exhibition of the crude preparation.

A number of drugs which act on certain nerve-cells also have a tendency to produce convulsions. These are nicotine, coniine, lobeline, gelsemine, and curarine. The effect is generally unimportant, and may be masked entirely by the peripheral effects, as is the case with curarine.

Tetanus Toxin is a body which can be isolated from tetanus cultures. The bacilli, having obtained entrance into the body, multiply locally and liberate the toxin, which is absorbed by the motor nerve-endings, and passes up these to the cord, where it appears to produce its action, but not in the same way as strychnine, for the tetanus toxin is destroyed in the process, and an emulsion of toxin and spinal cord is no longer poisonous to animals.

A number of drugs give rise to convulsions by an action on the medulla ; such are ammonium salts, picrotoxin, cicutoxin from the water hemlock (*Cicuta virosa*), œnanthotoxin from the water dropwort (*Œnanthe crocata*), and coriamyrtin from coriaria. The action of one of these (picrotoxin) will be described in further detail.

Picrotoxin is a neutral principle obtained from the seeds of *Anamirta paniculata*. Externally it is sometimes used as an ointment to kill pediculi.

If it is injected into a frog, violent clonic muscular contractions of the muscles are produced. They are still observed after removing the cerebral hemispheres, but are said to be modified when the optic lobes are also excised, and to cease or lose their characteristics when the medulla is removed. The spinal reflexes are increased even when the medulla is cut off from the cord, but in the higher animals at least there are no convulsive movements. So that although this drug has some action on the cord its chief effect is on the medulla.

It is difficult to say how convulsions can be produced by medullary stimulation, but it is certain that this stimulation does lead to clonic contractions of the muscles over the whole body, and further,

there can be no doubt that the effect is on the sensory cells in the medulla.

All the special centres in the medulla are excited as a result of this increased sensory appreciation. The heart-beat is slower, and the effect is central because the slowing is not obtained if the vagi are first severed. The excitation of the vaso-motor centre results in vaso-constriction, with a corresponding rise in blood-pressure. Picrotoxin has some further action on the heart since large doses tend to weaken the beat.

The vomiting centre is also excited: the effect can be shown to be on the centre since vomiting is obtained quicker by subcutaneous injection than when the drug is administered by the mouth.

The respiration becomes deeper and quicker. Death is produced by paralysis of the medulla in the later stages of intoxication.

The action of picrotoxin can be antagonised by the anæsthetics and narcotics. Chloral, for example, directly depresses the medulla and so tends to depress respiration, and to lower the blood-pressure by vaso-dilatation

Yohimbine is an alkaloid obtained from Yumbehoa bark in the Cameroons. It is employed as a sexual stimulant and is said to be superior to strychnine in that it increases pelvic reflexes only. It lowers blood-pressure by dilating vessels. Dose, $\frac{1}{20}$ to $\frac{1}{6}$ gr.

MATERIA MEDICA

Nux Vomica. Must contain not less than 1.25 per cent. strychnine. **Dose, 1 to 4 grs.** (6 to 25 cgrms.).

PREPARATIONS

1. **Extractum Nucis Vomicæ Liquidum.**—Standardised to contain 1.5 per cent. of strychnine. **Dose, 1 to 3 m.** (6 to 18 centimils).
2. **Extractum Nucis Vomicæ Siccum.**—Standardised to contain 5 per cent. of strychnine. **Dose, $\frac{1}{4}$ to 1 gr.** (16 to 60 mgrms.).
3. **Tinctura Nucis Vomicæ.**—Standardised to contain 0.1 per cent. of strychnine. **Dose, 5 to 15 m.** (3 to 10 decimils).

Strychnina. Dose, $\frac{1}{64}$ to $\frac{1}{16}$ gr. (1 to 4 mgrms.).

PREPARATION

Syrupus Ferri Phosphatis cum Quinina et Strychnina.—Each dr. represents $\frac{1}{32}$ gr. strychnine. **Dose, $\frac{1}{2}$ to 1 dr.**

Strychninæ Hydrochloricum. Dose, $\frac{1}{64}$ to $\frac{1}{16}$ gr.

PREPARATIONS

1. **Injectio Strychninæ Hypodermica** (0.75 per cent.). **Dose, 5 to 10 m.** (3 to 6 decimils) hypodermically.
2. **Liquor Strychninæ Hydrochloridi.**—1 per cent. Contains about 1 in 4 alcohol. **Dose, 2 to 8 m.** by the mouth; **1 to 4 m.** subcutaneously.

Picrotoxinum. Dose, $\frac{1}{100}$ to $\frac{1}{25}$ gr. (Not official.) $C_{30}H_{34}O_{13}$.

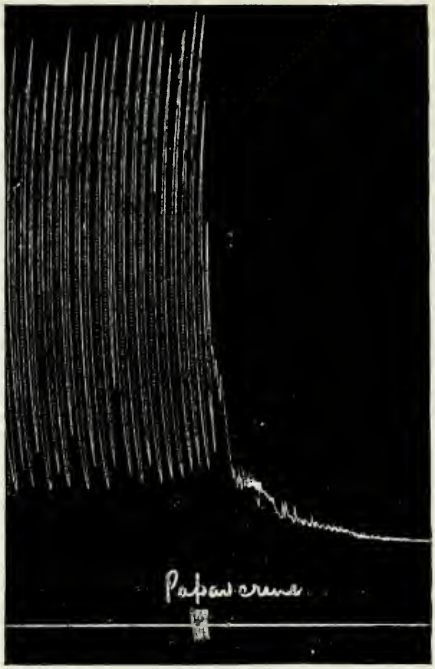


FIG. 32A.—ISOLATED RABBIT'S INTESTINE RECORDING LONGITUDINAL MOVEMENTS.

Shows the effect of administering papaverine. (3 mgrms. in 100 c.c. Ringer.)

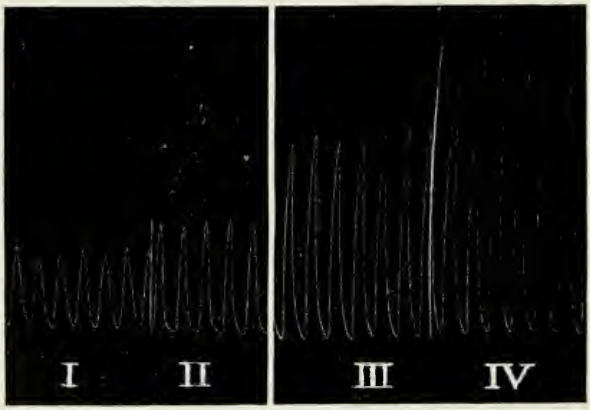


FIG. 32B.—ISOLATED RABBIT'S INTESTINE RECORDING LONGITUDINAL MOVEMENTS.

I represents normal movements; II, III, and IV were taken at intervals of five minutes after morphine. (3 mgrms. in 100 c.c. Ringer.)

To face p. 127.

CHAPTER VIII

THE VEGETABLE HYPNOTICS

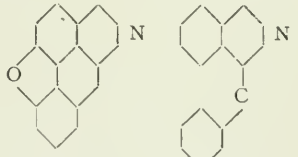
OPIUM

Opium is the dried milky juice of the poppy *Papaver somniferum*, obtained by incision from the unripe capsules of the plant and inspissated by spontaneous evaporation. About twenty-four hours after incision the exuded juice is partially dry and is then scraped off with blunt knives. Turkey and Persian opium are the varieties generally used in medicine, but opium obtained from Persia and India is unsuitable on account of the large percentage of narcotine that it contains. Opium used for the preparation of the tincture and extract must contain not less than 7.5 per cent. anhydrous morphine, and for other officially recognised purposes about 10 per cent.; if it contains more than this amount it may be diluted. Good Turkey opium usually yields from 12 to 18 per cent.

Good opium contains roughly one-fifth its weight of alkaloids. The most important of these is morphine, which exists in combination with meconic acid, then comes narcotine in very varying amounts from 2 to 10 per cent., codeine (methyl morphine) 0.3 to 2 per cent., and about 1 per cent. of other alkaloids such as thebaine, narceine, papaverine, &c. The other constituents are meconic acid about 5 per cent., resin gum, albumen, fat, sugar and salts.

$C_{16}H_{14}ONCH_3 \cdot (OH)_2$ (Morphine)
$C_{16}H_{14}ONCH_3 \cdot OH \cdot OCH_3$ (Codeine)
$C_{16}H_{12}ONCH_3(OCH_3)_2$ (Thebaine)

The constitution of morphine is important on account of the large number of derivatives which have been placed upon the market in recent years. The molecule consists of a tetra-hydro-phenanthrene derivative joined to another ring containing hydrogen.



Phenanthrene Pyridine Ring. Benzyl Isoquinoline Ring.

It will be seen from the formula that morphine contains two hydroxyl groups, one alcoholic and one phenolic, to which it will be necessary to refer later.

The opium alkaloids may be conveniently divided into two groups: (1) The phenanthrine-pyridine group which includes morphine codeine and thebaine, and (2) the benzyl-isoquinoline group which includes narcotine and papaverine. The members of both groups exert the same type of action on the central nervous system, but those of the first group tend, at first, to increase tone of plain muscle in the body, whereas those of the second always diminish both tone and movements (Fig. 32A).

Action

(1) *Depression of pain, perceiving centres in the cortex.*
(2) *Depression of Auerbach's plexus (constipation).*
(3) *Depression of medullary reflexes (respiratory sedative).*

When morphine is taken by the mouth it is absorbed readily, mainly from the small intestine, but partly from the stomach. It has a specific action on the nerve-cells of the brain, particularly the sensory cells. This action may be considered under three headings, the cerebral hemispheres, the medulla, and the cord.

Cerebral Hemispheres.—In the frog morphine has a characteristic action. Before considering this it must be remembered that when drugs acting on higher nerve-cells are under consideration, the strength of the action is in rough proportion to the relative development of the parts acted upon, and the smaller the brain the greater the dosage necessary: the quality of the action is not altered. In the frog, since the cerebral hemispheres are little more than protuberances from the third ventricle, one would not expect morphine to produce a very marked action in small doses, and it is found that frogs and all animals which have such small hemispheres are very tolerant to all the opium alkaloids, no effects following doses which would produce a decided action in man. If ¼ gr. of morphine is injected into the lymph-sac of a frog narcosis ensues, which is characterised by suppression of the functions of the brain inversely to their order of development. Spontaneous movements disappear first, the animal sits in a normal attitude and reacts to such stimuli as pinching like a normal frog, except that it will not avoid obstacles; it is, in fact, in the same condition as if its cerebral hemispheres had been removed by a surgical operation. With larger doses the animal shows evident signs of incoordination; it can no longer preserve its equilibrium, and when placed on its back, although it struggles, it fails to right itself; the effect is very similar to that which may be obtained by the removal of both the fore- and mid-brain. Still later the respiration stops and the spinal reflexes disappear, facts which show that the medulla

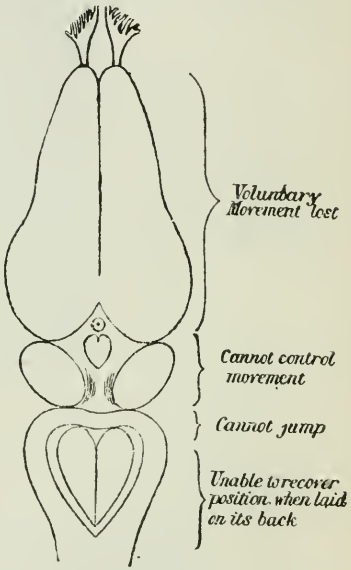


Fig. 33.—Diagram of the Dorsal Surface of a Frog's Brain.

The effects of removing the brain gradually from before backwards are shown on the right side of the diagram; they correspond with the progressive action of morphine and other vegetable narcotics which destroy the functions of the brain inversely to the order of their development.

and cord have been affected. After a lapse of several hours the frog begins to recover, its reflexes gradually return and soon become exaggerated, and the condition even culminates in strychnine-like convulsions with typical opisthotonus and intervals of quiescence and exhaustion. The action is produced—apparently in the same way that strychnine acts—on the sensory side of the cord. This characteristic effect of morphine on such a simple central nervous system is important, because in all higher brains the quality of action remains the same, but with proportional doses the quantitative narcotic action increases with the greater development of the cerebral hemispheres.

Morphine gives rise to a set of symptoms in mammals which can be explained most easily on the assumption that it depresses the various cerebral centres in the reverse order of their development; it forms a good example of the "law of dissolution." The higher psychical centres are the first to go. Thus attention, self-control, and judgment are lost early: any sustained mental effort becomes impossible and logical sequence in thought is lost. The condition of such a person may be demonstrated by getting him to write the history of some event, which he will do perhaps entirely to his own satisfaction, but which is in reality very poor stuff, showing little sequence or critical power. He has lost his controlling centres and has become more reflex, and so is at the beck and call of all kinds of extraneous stimuli. Sometimes delusions are present, such as indistinct and agreeable visions, and occasionally fantastic lights appear before the eyes, but these are certainly rare in the European. Perhaps the commonest delusion is an over-estimation of time and more rarely space; but these are more usual with certain other narcotics, particularly Indian hemp.

The administration of small doses of morphine to mammals sometimes produces a short period of excitement. This is shown by restlessness and sleeplessness: in the case of man there is an exuberance of imagination, the mind wanders from one subject to another, ideas flow rapidly and the picture presents the general exhilaration of intoxication. This excitement, as in the case of chloroform and alcohol, is due probably to the dissolution of the higher centres, to the absence of guidance of trains of thought, and not to a direct stimulation. The higher centres are certainly not stimulated at any period, since the time taken in the performance of elementary mental efforts, such for example as doing sums, is always increased. The patient has a desire to be left undisturbed, in a condition of dreamy abstraction and languid ease. Soon this gives place to a feeling of drowsiness, the eyelids droop, the body seems like lead, and he passes into a sleep often filled with dreams, but without tendency to voluntary movement. The patient may be roused from this sleep and induced to walk, although in a clumsy and awkward fashion, but without any signs of motor weakness. In correlation with this fact, it should be mentioned that in

animals the excitability to electrical stimuli of the cerebral motor area is unaffected by morphine.

All feelings and sensations and particularly those of pain are decidedly diminished. The reflexes gradually become less marked, tendency to cough is lessened, and touching the cornea produces little inconvenience. The stimuli arising from light, sound, and touch similarly give rise to diminished sensations. The whole action must be regarded as due to the depression of all sensory cells or, in other words, to a diminished consciousness, for consciousness is made up of a number of processes, ideas, feelings, wishes, resolutions, &c., and these are largely if not entirely reflex, *i.e.* they are called into being through sensations.

The hypnotics of the methane series produce general depression of all nerve-cells, motor as well as sensory, although there is reason to believe that the sensory cells are attacked first. Morphine has a specific effect on sensory nerve-cells alone, and no other drug relieves pain to the same extent.

Sometimes though rarely the excitement stage may be prolonged unduly, or the patient becomes maniacal: this condition is more usual in women and children possessing a highly emotional temperament than in men, but it is commonest in Malays and other Eastern races.

Cats (Felidæ) are peculiar among animals in that morphine gives rise at first to very marked restlessness and excitement; the animal rushes wildly about, its intelligence and perception are less, for it does not avoid obstacles, nor does it learn to avoid them by experience. This probably is not due to direct stimulation of the motor area, for, as already mentioned, there is little evidence that this area is affected by electrical stimulation after morphine, and what effect there may be is rather in the direction of depression. The excitement must be explained by a dissolution of the controlling centres. Why the cat should be affected in this way more than other animals it is difficult to say; but drugs which affect the central nervous system nearly always exhibit idiosyncrasies in different animals and not infrequently in animals of the same genus. To exemplify this it is necessary only to refer to the varieties of alcoholic intoxication in man, the lachrymose, pugnacious, hilarious, &c., all of which are determined by the man's habitual mode of thought, one type being constant for each individual.

The administration of morphine may give rise very occasionally to stimulation of the spinal cord, as shown by the increase in the reflexes, and this is more frequent in young animals and children: tetanic convulsions such as are obtained in frogs are never seen.

The question now arises why should this effect on the cord be so feebly developed in the mammal and yet so markedly in the frog. We have noted already that it is due to excitation of the posterior (sensory) part of the cord, and the mode of production is similar

in every way to that of strychnine. The simplest explanation of the action of morphine is that it produces a depression of the sensory cells throughout the body: with small doses the psychical centres only are affected, and with large doses the lower centres and cord are attacked. In those animals in which the cerebral hemispheres are poorly developed, such as the frog, relatively very large doses of morphine are necessary to produce a decided depressing effect on the lower centres, the mid-brain and cord, so large indeed that such doses administered to man in anything like proportional amounts would produce death by paralysing the medulla. If very large doses of morphine are given to mammals which are kept alive by means of artificial respiration, increased reflexes or even convulsions may be observed. One explanation of the action of morphine on the cord is that, as the depression of the cells of the cord passes

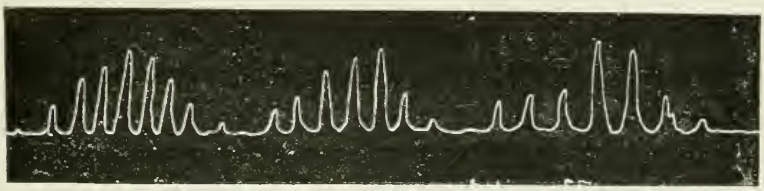


FIG. 34.—DOG. CHEYNE-STOKES RESPIRATION PRODUCED AFTER A LARGE DOSE OF MORPHINE (1½ gr.).
Upstroke = inspiration.

off, they become hyper-sensitive and so give rise to convulsions. Another explanation which has been offered is the supposition of paralysis of the motor nerve-cells, and at the same time excitation of the sensory cells. The first symptoms of the drug according to this view are due to the effect on the anterior root being the most marked, and the latter effect to the sensory portion being most affected and more than counterbalancing the motor effect. This is a pure speculation without any evidence in its support.

The greater the development of the cerebrum the smaller is the tendency of morphine to produce any decided excitation of the cord, and the smaller is the relative dose. Frogs recover after enormous doses of morphine although respiration may have ceased for several hours.

In man larger doses (1 to 2 grs.) lead to a deeper sleep, from which the patient is awakened only with difficulty; it is followed later by coma. A dog after a large dose shows all the signs of diminution of sensory impressions. It lies in a crouching attitude from partial paralysis of the hind-limbs, and is in a condition resembling that seen after ablation of the motor areas.

To sum up, morphine depresses all sensory nerve-cells in the brain and only very slightly the motor cells. In the cord there is at first a similar depression, which may be followed by some hyper-excita-

bility, as shown by twitchings, tremors, or even sometimes by tetanic convulsions.

Even small doses of morphine depress the **respiratory centre** in the medulla. The respiration becomes slower, and the inspiration is somewhat prolonged so that it is deeper than usual; the sum total of these two factors is to diminish the respiratory exchange. In a resting rabbit the air expired in thirty seconds averages about 200 c.c. If 0.01 gram morphine hydrochloride is administered as an injection the average soon falls to about 90 c.c., and in man a similar condition obtains, though not so exaggerated as in the example given. In larger doses the respiration becomes very shallow, and before death frequently assumes the Cheyne-Stokes type. The explanation of this action on the medulla is further discussed under Heroine.

Morphine is commonly employed to stop useless coughing, and this it does by diminishing reflex irritation.

The natural hormone stimulating the respiratory centre is CO_2. Under morphine animals react to CO_2 like normal animals, the respiration increasing in depth and rate. In animals under the influence of the ordinary anæsthetics or hypnotics, CO_2 produces a diminished effect. The explanation may be that morphine acts only on cells receiving nerve impulses (sensory), whereas the indifferent hypnotics act on all nerve cells.

Peripheral Effects.—Morphine has no action on motor and very little on sensory nerve-endings, so that the local application of this drug in any form is irrational, and any good results which may ensue are probably the result of absorption.

The acuity of all sensations is diminished. This may be observed readily in the skin by measuring the shortest distance at which the two points of a pair of dividers can be recognised separately. When a number of control experiments have been performed it is found that after a dose of morphine this distance is decidedly increased. The effect of the drug begins a few minutes after the injection, and lasts for about twelve hours.

Morphine has little action on the secretions, but such as it has leans towards depression; the perspiration is an exception, however, for this is increased as a result of the cutaneous vaso-dilatation; from the same cause rashes are also sometimes seen.

The secretion of urine is uninfluenced by morphine, and this drug would form a valuable hypnotic in renal disease were it not for the constipation it induces.

Circulation.—Morphine has little effect on the heart or vessels. It slightly depresses the medulla, and, like many other drugs having this action, for example the hypnotics of the methane series, it dilates the skin-vessels whilst producing little effect on other vessels, such as the splanchnic: in consequence it hardly affects blood-pressure. The dilatation of the cutaneous vessels is accom-

panied by a feeling of warmth, and occasionally by intolerable itching and rashes.

Many allied alkaloids produce decided vaso-dilatation of all vessels, with a corresponding fall in blood-pressure. This has been shown already to depend upon the depression of certain sympathetic nerve-cells, particularly those on the course of the splanchnic fibres, so that the effect is produced in the same way as it would be by cutting through the splanchnic nerves. The four alkaloids—morphine, codeine, apomorphine, and apocodeine—produce, in the order mentioned, an increasing fall of blood-pressure, and this fall corresponds exactly to their relative power of paralysing these nerve-cells.

Alimentary Canal.—Morphine and its allies have two distinct actions on the alimentary canal. The one is obtained whilst the drug is in the circulation, and depends on a depression of certain nerve-cells. The other and more important is obtained during the excretion of the drug into the gut, and is a direct action on the gut wall. In order to understand this first action it will be advantageous to consider once again the four alkaloids, apocodeine, apomorphine, codeine, and morphine. All these produce some purgation in dogs and cats, but the action is much the greatest with apocodeine, less with apomorphine, still less with codeine, and least with morphine. It falls off in a regular sequence in precisely the same way as the vaso-dilatation ; and running parallel with these two effects is their depressant action on sympathetic nerve-ganglia.

When a comparatively large dose of any of these drugs suddenly reaches the blood-stream it increases the tonus and peristaltic movements of the plain muscle in the alimentary canal. This is readily seen in mammals by direct observation of the intestines when the drug is injected directly into the circulation. A subcutaneous injection in the cat or dog induces purgation generally with vomiting in a few minutes, and in man a big injection of morphine may induce nausea, vomiting, and, in rare cases, even purging, whilst apocodeine invariably produces one or more stools.

The action is not peripheral, since if these alkaloids are painted directly on living mammalian gut they stop all peristaltic movements; nor is it entirely on the brain, medulla, or cord, since the drugs still increase peristaltic movements after section of the splanchnics and vagi. It is probable that depression of the cells of the splanchnic is responsible for the effect. The splanchnic nerve is the inhibitory nerve to the gut, and just as nicotine and coniine produce initial inhibition of peristaltic movement by stimulation of the cells on the course of these fibres, so the drugs under consideration augment peristaltic movement by diminishing inhibitory influences. Indeed, the effect is analogous to the excitement after alcohol, where the hyper-activity is due to depression of inhibition.

The opium alkaloids in the same way augment the normal movements of the stomach and the tonic contraction of the cardiac end.

However interesting these initial augmented peristaltic movements may be, the opium alkaloids are given to produce the contrary effect, to check excessive peristalsis. It is only when the drug rapidly reaches the circulation that an initial augmentation of the movements is observed. If morphine or other opium alkaloid be injected into a loop of intestine, suitably ligatured off from the rest of the intestine, of a decerebrate animal, vagal stimulation soon ceases to influence this portion of the intestine, whilst it still augments movements in the rest of the intestine. The ligatured portion still responds to muscle-poisons like lead or barium. The paralysis is probably, therefore, in some part of the peripheral nervous mechanism, and in support of this is the fact that pilocarpine, a drug which acts on nerve-endings, has no effect when applied directly to the paralysed gut, but produces violent contractions if painted on normal portions. Morphine is entirely excreted by the alimentary canal, even when it is injected, and it is probably during its excretion that it mainly affects the peripheral nervous mechanism and so produces diminution of the normal peristaltic movements.

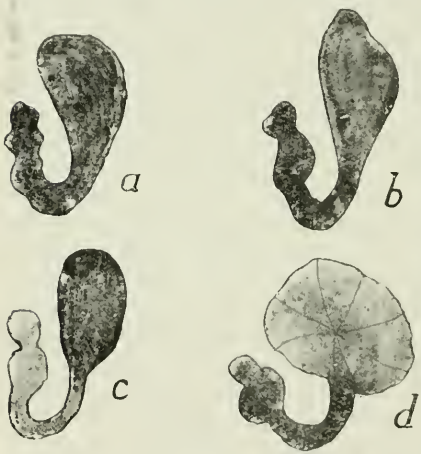


FIG. 35.—X-RAY PHOTOGRAPHS.

Cat's stomach containing bismuth and potato purée. *a*, Normal; *b*, 22 mins. after injection of morphine; *c*, 1 hour after; *d*, 3 hours after. Note the food remaining in the distended fundus, while the middle portion of the stomach is contracted and the pyloric portion is also contracted, but undergoing peristaltic movements. (Magnus.)

On the *stomach* of man small doses of morphine have little effect; sometimes they increase slightly gastric motility; larger doses, $\frac{1}{4}$ gr. or more, cause spasm of the pyloric end and relaxation of the fundus, so that the gastric contents may leave the stomach several hours late. This effect will tend towards constipation; it will probably allow gastric fermentations by yeasts and other organisms to proceed and it will delay the absorption of drugs.

X-ray experiments on man afford some clue as to the part of the alimentary canal on which morphine acts in suppressing excessive peristalsis or causing constipation. Food is retained longer in the stomach (Fig. 35), but the principal effect is on the cæcum and ascending colon, the movements of which are so diminished as to cause considerable delay in the passage of food. The small intestine is less affected.

In the treatment of diarrhœas, however, opium is always superior to morphine, partly, no doubt, because absorption is delayed by the colloidal nature of the drug which remains longer in contact with the intestine; but also, perhaps, on account of the isoquinoline derivatives which induce immediate relaxation of all plain muscle.

Metabolism and Tolerance.—We have seen already that the absorption of oxygen is considerably diminished after morphine; the carbonic-acid output is diminished also, although not to the same relative extent as the oxygen. As a result, the amount of carbonic acid present in the blood is usually increased slightly. Metabolism is lessened, no doubt, on account of the general quiescence. In consequence of these combined effects less nitrogen is excreted in the urine.

Morphine is excreted by the whole alimentary tract. About five minutes after a small hypodermic injection it can be detected in the contents of the stomach. Only the merest trace is excreted by the urine.

If a sub-lethal hypodermic injection of morphine is given to a dog about 70 per cent. of this can be extracted from the fæces. If the same dose is administered daily the amount excreted gradually diminishes until little or no morphine is excreted at all. Moreover, in proportion as the morphine ceases to be excreted it loses its action, and in order to produce the same effect on the animal as that obtained by the first injection, ever increasing doses must be given. If the dog under experiment is killed at this stage no morphine can be found in any of the tissues. It is, therefore, certain that the living tissues are capable of destroying this alkaloid, and it is very probable that habituation to morphine and the increasing doses necessary to satisfy the morphomaniac are due to the increased capacity of the tissues to destroy the alkaloid. An analogous example, though less marked, is that of alcohol, in which the habitué can oxidise more than the novice.

The bodies which give rise to the characteristic odour of opium are excreted mainly by the urine, but also to some extent by the breath and perspiration.

Toxicology.—After taking 1 to 2 grs. of morphine sleep is quickly induced; it becomes deeper and deeper, and passes into coma. In well-marked cases the reflexes disappear, the respiration becomes slower and shallower, and is often no quicker than two or three per minute; it may assume the Cheyne-Stokes type. Consequently the patient is more or less cyanotic. Blood-pressure falls, though not greatly, the skin is cold and moist with perspiration, and the pupils are contracted almost to a pin-point. Death occurs from asphyxia. Very occasionally death is preceded by convulsions; these are more common after opium than morphine, and may be due to the drug containing a large percentage of narcotine.

The diagnosis between opium poisoning, alcoholic intoxication, and hæmorrhage into the brain must be determined by the history, the smell of the opium, and the contracted pupils, although in hæmorrhage into the pons the latter sign is also present.

The opium habit shows itself in two ways: in some habitués large quantities are necessary to produce the required result, whilst in others a long interval is requisite for the drug to take effect. The latter action is attributed to a diminution in absorptive power. The habit is common in India, where 5 to 10 grs. of opium taken by the mouth form a common daily dose, and in China, where about 10 per cent. of the males smoke opium. Europeans, with whom the habit is very much rarer, usually employ injections of morphine. When once the habit is formed, deprivation of the drug leads to sleeplessness, mental misery, and lack of physical energy, whilst diarrhœa, tremors, and other nervous symptoms ensue, which all disappear when the craving is satisfied. After prolonged over-indulgence the mental powers become enfeebled, the moral faculties perverted, and the motor centres show signs of degeneration.

The general use of opium in India led to a Royal Commission (1895), which reported that moderate indulgence led to no injurious effects and did not shorten life; but that, on the contrary, it tended to ward off sickness and lessened the discomfort consequent on poor food and gastro-intestinal and malarial diseases. On the Chinese the effect of smoking the drug is to produce slight excitement followed by a feeling of ease and satisfaction. Europeans, at all events at first, derive little satisfaction from the smoking, but with practice they likewise become slaves to the habit.

The treatment of acute opium poisoning should consist, in the first place, in washing out the stomach with a 0.1 per cent solution of potassium permanganate, which oxidises morphine and renders it inactive. This may be repeated three or four times at intervals, because the drug continues to be excreted into the stomach. As death results from respiratory failure every means should be taken to combat this by stimulating the medulla. This may be attempted reflexly by the faradic current or flicking the body with a cold damp towel, but artificial respiration if necessary with oxygen should be employed early. Lastly, drugs antagonistic to morphine which stimulate the centre may be injected, such as caffeine, strychnine, and atropine. Any of these are antagonistic to morphine in that they induce vaso-constriction by acting upon the medulla, and therefore tend to raise the blood-pressure and stimulate the respiratory centre. The dilatation of the pupils induced by atropine is not a true antagonistic effect to the pin-hole pupils of morphine, because the former drug acts peripherally on the nerve-endings of the third, whilst the action of the latter is central.

Comparison of the Different Opium Alkaloids

All the opium alkaloids produce nervous depression, which is succeeded by a more or less pronounced stage of convulsions. The depression is an effect beginning upon the psychical centres in the brain and working downwards in an evolutionary order, following the law of dissolution. The convulsions are due to a strychnine-like action on the cord, and are a separate and distinct feature. These alkaloids may be roughly classed according to which of thes actions predominates:—

Morphine (most narcotic).
Papaverine.
Codeine.
Narcotine.
Thebaine.
Laudanine (most convulsant).

Morphine is the most narcotic and analgesic; increased reflexes or spasmodic twitchings are extremely rare during its administration. **Codeine** (methyl morphine) in small doses produces a slight but distinct narcosis, but the sleep is not so sound and restful as with morphine, and is followed occasionally by restlessness and increased reflexes. Excitement and muscular twitchings follow the administration of large doses, and when it is injected into animals spasmodic twitchings are more readily obtained than with morphine.

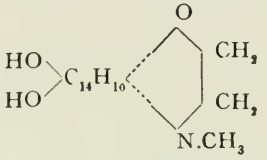
The depressant action of codeine on sympathetic nerve-cells is greater than that of morphine, and therefore there is a larger fall of blood-pressure from vaso-dilatation and an augmentation of the movements of plain muscle; the injection of the drug subcutaneously into man has given rise to vomiting and occasionally to purgation. Codeine is less likely to give rise to a habit than morphine, and as it has the same action on the sensory nerve-cells it is used to stop useless and chronic cough. Unlike morphine codeine is not destroyed in the body, but is excreted by the kidneys. This is a fundamental difference for which at present no explanation is forthcoming.

Papaverine has an action very similar to that of codeine. Small doses induce sleep, which does not become deeper as the dose is increased, but is followed by a stage of increased reflexes. Papaverine relaxes all smooth muscle, including the arterioles. It is sometimes employed to diminish high arterial blood-pressure in arterio-sclerosis and renal disease. It has also been used to relax the bronchioles in spasmodic asthma.

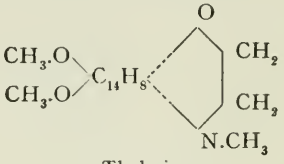
Thebaine may be taken as typical of the more convulsant alkaloids. Like the other alkaloids it possesses both a narcotic and convulsant action, but its narcotic action is masked largely by its effect on the cord. The first result of an injection into animals

is usually well-marked strychnine-like convulsions. Morphine and thebaine are not diametrically opposite in action, indeed the kind of action is the same in both cases; but whereas the depression of sensory cells of the brain is the characteristic feature after morphine, whilst the cord is comparatively little affected, thebaine has a very marked action on the cord, which masks the cerebral effect.

Thebaine differs from morphine chemically in possessing two CH_3 groups in place of the two hydrogens of the hydroxyl, and in containing two hydrogens less in the remaining radicle.



Morphine.



Thebaine.

Narcotine is less poisonous than morphine or thebaine: as regards quality of action it occupies a position between codeine and thebaine. When it is administered to animals the depressant action on the cerebral hemispheres is not well marked, because of the early onset of cord symptoms. On plain muscle its action is like papaverine.

Artificial Alkaloids of the Morphine Group

In recent years a number of artificial morphine derivatives, prepared in the laboratory, have been recommended as substitutes for morphine. One benzene ring of the morphine molecule contains two (OH) groups, one alcoholic and one phenolic; the most interesting derivatives pharmacologically are those obtained by modifying these two groups. Three such compounds only require mention: *Dionine*, the hydrochloride of ethyl morphine, in which the hydrogen of the phenolic OH is replaced by C_2H_5. In action it closely resembles that of codeine, which is methyl morphine. *Peronine* is the hydrochloride of benzoyl morphine, in which the hydrogen of the phenolic OH is replaced by $C_6H_5CH_2$; and *heroine* has the hydrogens of both (OH) groups replaced by the acetyl (CH_3CO) radicle: it is now official under the name diamorphine.

These substitution compounds should not be confounded with the morphium and strychnium compounds, which are addition compounds. Unfortunately methyl-strychnine is often referred to when methyl-strychnium chloride is really what is meant.

The object in forming these bodies has been to produce a sedative resembling morphine, which will relieve pain without having the depressing action of morphine on the respiratory centre. For this

purpose dionine, heroine, and codeine are the rivals. All these three are employed to diminish useless cough and alleviate other forms of peripheral irritation. The introduction of the acid and alkyl groups into the morphine molecule weakens the narcotic, but strengthens the convulsant action and increases the depression of the sympathetic nerve-cells.

All these drugs have a characteristic action on respiration; they slow the rate, but increase the depth; so that the total respiratory exchange is little altered. The action is not a simple stimulation of the centre, such as hydrocyanic acid or caffeine might produce, nor is it a simple depression of motor cells such as chloral might induce.

For the normal performance of the respiratory functions the arrival of afferent impulses at the centre is necessary, and if as many afferent nerves to the medulla as possible are cut through with the knife the respiratory movements become slower and deeper. Now we know that morphine specially depresses the afferent impulses, probably at the sensory nerve-cells, and we believe that the drugs under consideration produce their effects by limiting the afferent impulses. Hence the automatic activity of the centre is diminished, but when an explosion occurs it is more violent than normal, perhaps in the same way that these drugs exaggerate all spinal reflexes. Dionine and peronine like codeine, are not destroyed by the body but are excreted by the urine. Dionine is sometimes employed to procure absorption of inflammatory thickenings in the eye. If a little is distilled into the eye, it causes conjunctivitis, swelling and exudation of serum. In a few hours this inflammatory fluid is absorbed and with it often morbid products; for this reason it is sometimes used in inflammatory thickenings, keratitis, iritis and the like.

Heroine (diamorphine) has doubtful advantages over codeine in the treatment of cough. It is partly oxidised in the body like morphine, but unlike morphine is excreted by the kidneys. It is perhaps the easiest drug with which to form a habit, being less constipating than morphine, but with the formation of a habit it is increasingly destroyed by the body. In recent times this habit has sometimes been formed by its use as a snuff.

MATERIA MEDICA

Opium. Dose, ½ to 2 grs. (3 to 12 ctgrms.).

Preparations

1. **Tinctura Opii.**—Laudanum. Standardised to contain 1 per cent. morphine.
   Dose, 5 to 15 m. (3 to 10 decimils) for repeated, **20 to 30 m.** (12 to 18 decimils) for single administration.
2. **Tinctura Camphoræ Composita.**—Paregoric. Tincture of opium, benzoic acid, camphor, oil of anise, alcohol. Contains 0.005 grm. of morphine in 10 millilitres.
   Dose, ½ **to 1 dr.** (2 to 4 mils).
3. **Tinctura Opii Ammoniata.**—Is a somewhat similar preparation, containing ammonia instead of camphor.
   Dose, ½ **to 1 dr.** (2 to 4 mils).
4. **Extractum Opii Siccum.**—Opium, distilled water. Standardised to contain 20 per cent. of morphine.
   Dose, ¼ **to 1 gr.** (16 to 60 mgrms.).
5. **Extractum Opii Liquidum.**—Standardised to contain 0.75 per cent. of morphine.
   Dose, 5 to 30 m. (3 to 18 decimils).
6. **Pilula Plumbi cum Opio.**—Opium, 1; lead acetate, 6. *Strength:* 1 in 8.
   Dose, 2 to 4 grs. (12 to 25 ctgrms.).
7. **Pilula Saponis Composita.**—Opium, hard soap. *Strength:* 1 in 5.
   Dose, 2 to 4 grs. (12 to 25 ctgrms.).
8. **Pilula Ipecacuanhæ cum Scillâ.**—Compound ipecacuanha powder, 3; squill, 1; ammoniacum, 1. *Strength:* 1 in 20.
   Dose, 4 to 8 grs. (25 to 50 ctgrms.).
9. **Pulvis Ipecacuanhæ Compositus.**—Dover's powder. Powdered opium, 1; ipecacuanha, 1; potassium sulphate, 8. *Strength:* 1 in 10.
   Dose, 5 to 15 grs. (3 to 10 dcgrms.).
10. **Pulvis Cretæ Aromaticus cum Opio.**—Opium, aromatic chalk powder. *Strength:* 1 in 40.
    Dose, 10 to 60 grs. (6 to 40 dcgrms.). For a child aged one year, ½ **to 1 gr.**
11. **Pulvis Kino Compositus.**—Opium, 1; kino, 15; cinnamon, 4. *Strength:* 1 in 20.
    Dose, 5 to 20 grs. (3 to 12 dcgrms.).
12. **Pulvis Opii Compositus.**—Opium, black pepper, ginger, caraway, tragacanth. *Strength:* 1 in 10.
    Dose, 5 to 15 grs. (3 to 10 dcgrms.).
13. **Suppositoria Plumbi Composita.**—Powdered opium, 1; lead acetate, 3; oil of theobroma, 11. 1 gr. of opium in each.
14. **Linimentum Opii.**—Equal parts of tincture of opium and soap liniment.
15. **Unguentum Gallæ cum Opio.**—Powdered opium and ointment of galls. *Strength:* 7.5 per cent.

Morphinæ Hydrochloridum.—Soluble to about 4 per cent. in water and 2 per cent. in alcohol. **Dose,** $\frac{1}{8}$ **to** $\frac{1}{2}$ **gr.** (8 to 30 mgrms.).

PREPARATIONS

1. **Liquor Morphinæ Hydrochloridi.**—*Strength :* 1 per cent.
   Dose, 10 to 60 m. (6 to 36 decimils).
2. **Suppositoria Morphinæ.**—Each contains $\frac{1}{4}$ gr. of morphine hydrochloride.
3. **Tinctura Chloroformi et Morphinæ Composita.**—Chloroform, dilute hydrocyanic acid, tincture of capsicum, tincture of Indian hemp, and morphine hydrochloride 1 per cent.
   Dose, 5 to 15 m. (3 to 10 decimils).
4. **Trochiscus Morphinæ.** — Morphine hydrochloride, $\frac{1}{3\frac{1}{2}}$ gr. (0.002 grm.); with a tolu basis.
5. **Trochiscus Morphinæ et Ipecacuanhæ.**—Morphine hydrochloride, $\frac{1}{3\frac{1}{2}}$ gr. (0.002 grm.). ; with a tolu basis.

Morphinæ Tartras.—Soluble to about 9 per cent. in cold water.
Dose, $\frac{1}{8}$ **to** $\frac{1}{2}$ **gr.** (8 to 30 mgrms.).

PREPARATIONS

1. **Injectio Morphinæ Hypodermica.**—A $2\frac{1}{2}$ per cent. solution.
   Dose, 5 to 10 m. (3 to 6 decimils).
2. **Liquor Morphinæ Tartratis.**—A 1 per cent. solution in alcohol and water.
   Dose, 10 to 60 m. (6 to 36 decimils).

Morphinæ Acetas.—Soluble to nearly 40 per cent. in water.
Dose, $\frac{1}{8}$ **to** $\frac{1}{2}$ **gr.** (8 to 30 mgrms.).

PREPARATION

Liquor Morphinæ Acetatis.—A 1 per cent. solution in water, containing some alcohol and a little acetic acid.
Dose, 10 to 60 m. (6 to 36 decimils).

Codeina.—Soluble to about 1 in 80 of cold water.
Dose, $\frac{1}{4}$ **to 1 gr.** (16 to 60 mgrms.).

Codeinæ Phosphas.—Soluble to about 25 per cent. in water.
Dose, $\frac{1}{4}$ **to 1 gr.** (16 to 60 mgrms.).

PREPARATION

Syrupus Codeinæ Phosphatis.—*Strength :* 0.5 per cent. (weight in volume).
Dose, $\frac{1}{2}$ **to 2 drs.** (2 to 8 mils).

Diamorphinæ Hydrochloridum. Dose, $\frac{1}{2\frac{1}{5}}$ **to** $\frac{1}{8}$ **gr.** ($2\frac{1}{2}$ to 8 mgrms.).

Dionine. (Not official.) **Dose,** $\frac{1}{4}$ **to** $\frac{3}{4}$ **gr.**

CANNABIS INDICA

Cannabis indica consists of the dried flowering tops of the female plant *Cannabis sativa*, which has been grown in India, and from which the resin has not been removed. If the plant is transported

from India to temperate climates it loses its narcotic properties, although the resinous substance is still elaborated. The drug as prepared in India is known in three forms: *bhang*, the dried leaves of either sex; *charas*, the resinous exudation; and *gánjá*, the dried flowering tops coated with resin. The term "hashish" is a collective name, applied to almost all preparations of the plant.

The active principle is an oily substance, which can be removed by extracting the resinous material with petroleum spirit. The extract so obtained is evaporated to dryness and subjected to fractional distillation, when the part distilling over between 210° and 240° C. is found to have a definite and constant composition, and to have the characteristic action of the crude drug. This substance, cannabinol ($C_{21}H_{30}O_6$), is a pale yellow syrup, and is remarkable in that it contains no nitrogen: in contact with the air it readily becomes decolorised from oxidation, and simultaneously loses its toxicity. The crude drug also contains some substances allied to choline and muscarine, as well as a little essential oil.

Hemp resin of different seasons and places contains very different amounts of cannabinol, so that the amount of resin forms no criterion as to the toxicity of the drug. Some means of standardising is therefore a necessity. This may be done (1) by estimating the amount of cannabinol in a given sample, (2) by experiments on animals. It must not, however, be forgotten that the resin slowly deteriorates by contact with air. When hemp is administered by the mouth it is probably absorbed in the small intestine. The time before the effects of the drug are seen is very variable, but on the average it is about half an hour. If the drug is smoked the characteristic symptoms come on almost immediately, but do not last so long. Hemp has little or no action on the movements of the alimentary canal.

Central Nervous System.—The main action of the drug is on the central nervous system. It first gives rise to excitement. This is observed typically in the dog, which rushes wildly about, exhibits circus movements, and constantly barks. In man there is a series of symptoms which are comparable in many ways with those of alcohol: the patient is restless and noisy, he laughs immoderately and out of proportion to the cause, and is less shy and freer in his speech, whilst his manners no longer conform to those of polite society. Now, as in the case of alcohol, there is reason to believe that this excitement of the motor areas and other lower centres in the brain is not the result of direct stimulation of these, but is due to depression of the highest and controlling centres. At all events, there is a depression of the highest centres, and this is shown by diminished efficiency in the performance of mental work, by inability to concentrate attention, and by feeble judgment. Like alcohol the patient, as a result of his feelings, regards cannabis as a decided "stimulant," and his uncontrolled fancies he regards as the cerebration of an exalted brain: introspection is useless

as evidence of stimulation. If the environment is suitable, the patient sooner or later sinks into a condition of dreamy and languid contentment, followed by sleep. Animals in this stage often exhibit a changed disposition—for example, cats no longer show their antipathy to dogs, but even rub up against them. Hallucinations are a common feature of this intoxication. Ideas of an impossible character flicker across the mental horizon—the patient is unable to control them, and he does not recognise that they are ridiculous.

Undoubtedly the two most important illusions are those of time and space. Time is not estimated correctly, minutes seem to be as hours. We estimate time by successive mental impressions, thus a man who for the first time witnessed an execution believed he had been in the jail at least an hour, whereas in reality he had been there only a few minutes. In the same way, the uncontrolled and fleeting thoughts and impressions during hemp intoxication lead to an over-estimation of time. Space may be over-estimated also, although this is less common. These illusions are seen sometimes with morphia and mescal, but they are most characteristic in the case of hemp. Moderate inhalation of hemp smoke is said to be refreshing and soothing, and to relieve mental fatigue and exhaustion. During hemp intoxication certain physical signs are also evident. There is always some muscular weakness, incoordination of movement, and slurring of speech. In animals there are curious rocking movements, which are due to inco-ordination, followed later by pronounced loss of power or even paralysis of the hind-limbs. These effects are in contrast with morphine, which in moderate doses produces no effect on the motor functions. Like morphine, hemp diminishes the perception of pain and produces partial anæsthesia of the skin, so that animals become indifferent to position. In the early stages of intoxication the reflexes may be somewhat increased, although later they are decidedly depressed.

Respiration is influenced but little by cannabis in medicinal doses. During the excitement stage it is somewhat accelerated, and during deep narcosis it is slower and more pronounced.

Heart and Circulation.—There is always a considerable increase in the pulse-rate when the drug is smoked; it is possible this may be due in part to the excitement. When the drug is taken by the mouth the quickening is less noticeable, and during deep narcosis the heart is slowed very decidedly.

MATERIA MEDICA

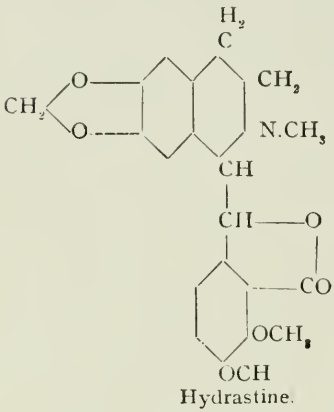
Cannabis Indica.

PREPARATIONS

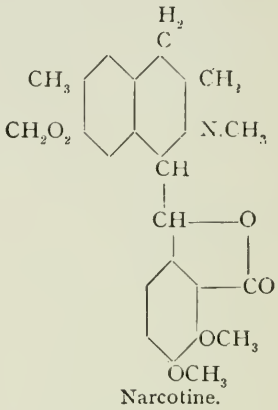
1. **Extractum Cannabis Indicæ.**—Alcoholic.
   Dose, $\frac{1}{4}$ to 1 gr. (16 to 60 mgrms.).
2. **Tinctura Cannabis Indicæ.**
   Dose, 5 to 15 m. (3 to 10 decimils) in mucilage or wine.

HYDRASTIS

Hydrastis rhizome is obtained from *Hydrastis canadensis.* It contains several alkaloids: hydrastine, 2 to 4 per cent.; berberine, 3 to 4 per cent.; and canadine (tetrahydro-berberine). Hydrastine is closely related to narcotine, as is shown by the following formulæ:—



Hydrastine.



Narcotine.

It is decomposed into opianic acid and hydrastinine when exposed to oxidising agents.

$$\underset{\text{Hydrastine.}}{C_{21}H_{21}NO_6} + H_2O + O = \underset{\text{Opianic acid.}}{C_{10}H_{10}O_5} + \underset{\text{Hydrastinine.}}{C_{11}H_{13}NO_3}$$

Narcotine undergoes a somewhat simila· decomposition into opianic acid and cotarnine:—

$$\underset{\text{Narcotine.}}{C_{22}H_{23}NO_7} + H_2O + 2O_2 = \underset{\text{Opianic acid.}}{C_{10}H_{10}O_5} + \underset{\text{Cotarnine.}}{C_{12}H_{15}NO_7}$$

Berberine has little action and canadine is present only in very small quantities, so that the action of hydrastis is that of the alkaloid hydrastine.

The pharmacology of hydrastis is unsatisfactory. In the mouth, on account of the berberine present, it has the action of the bitters. Hydrastine is absorbed readily from the stomach and intestines, and in big doses may produce vomiting and diarrhœa, but it is not certain how these effects are obtained.

Central Nervous System.—The typical action of the drug is exerted on the central nervous system, and closely resembles that of thebaine or narcotine. The first effect is usually slight depression of the mental faculties associated with some drowsiness; but this action is unlike morphine in that the excitability of the motor areas to electrical stimulation is at the same time diminished, a fact which has led to the employment of the drug in epilepsy.

The medulla is stimulated, and, in consequence, the following effects ensue:—(1) The respiration is deeper and quicker, the action

being equally well seen after section of the vagi; (2) the heart is slowed, but only so long as the vagi remain intact, again showing that the action is central; (3) the blood-pressure rises from vaso-constriction and this must be central also, since a rise is not obtained after cutting the cord below the medulla.

The spinal cord is affected in much the same way as by thebaine. Reflexes are increased and there are irregular twitchings of the muscles, whilst after very large doses typical strychnine-like convulsions are produced.

Circulation.—Small doses of hydrastine raise the blood-pressure and slow the heart, but the output is little affected, and the rise in blood-pressure is, as we have already seen, due to stimulation of the medulla. Large doses quicken the heart from depression of the vagus centre or the nerve-cells on the course of the vagus. In the frog particularly, these cells can be easily paralysed, as is seen from the fact that after using the drug stimulation of the vagus produces no slowing of the heart, whilst excitation of the sinus still gives a typical inhibition. Large doses directly depress the heart muscle.

Nerve-endings and Muscle. — Hydrastine has no action on sensory nerve-endings, but, like thebaine, it paralyses the motor nerve-endings in the frog. In mammals the medulla is paralysed, though the animal dies long before this stage is reached, but if the animal is kept alive by artificial respiration the effect can be obtained.

Hydrastine has been used to produce constriction of peripheral vessels in hæmorrhage, as a cholagogue, and to contract the uterus; but it is probably useless in all these conditions. It is excreted unchanged in the urine. Dose, ½ to 1 gr. in a pill.

HYDRASTININE is an artificial alkaloid obtained by oxidising hydrastine. Its effect on peripheral vessels is much greater than that of hydrastine, but it is less depressant to the heart, and does not cause convulsions: its principal action is probably its effect in increasing uterine tonus. Dose, ½ to 1½ grs. hypodermically.

COTARNINE, the hydrochloride of which is sometimes called stypticine, has much the same action as hydrastinine. It is used more especially for uterine hæmorrhage.

MATERIA MEDICA

Hydrastis Rhizoma.

PREPARATIONS

1. **Extractum Hydrastis Liquidum.**—Must contain 2 per cent. of hydrastine.
   Dose, 5 to 15 m. (3 to 6 decimils).
2. **Tinctura Hydrastis.**
   Dose, ½ to 1 dr. (2 to 4 mils).

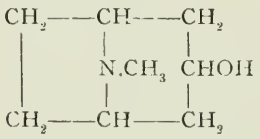
CHAPTER IX

LOCAL ANÆSTHETICS

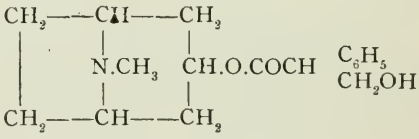
COCA

COCA LEAVES are obtained from *Erythroxylon coca*, a plant which is cultivated in Bolivia and Peru, and the dried leaves are imported into this country. They contain a variable amount of alkaloid, averaging 0.5 per cent., the Bolivian variety containing more than the Peruvian.

Two-thirds of the total alkaloid is cocaine, which chemically is methyl-benzoyl-ecgonine, and which on hydrolysis will therefore yield methyl alcohol, benzoic acid, and ecgonine. The latter body is closely related to tropine, and the relationship between them is shown below :—



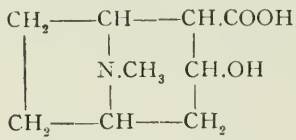
Tropine.



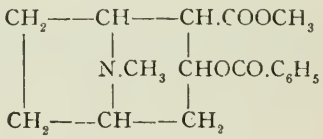
Tropine. Tropic Acid.

Atropine.

If the acid radicle is removed the mydriatic action of atropine is lost.



Ecgonine (not anæsthetic).



Cocaine (local anæsthetic).

If either the acid radicle or the CH_3 group is removed from cocaine the local anæsthetic action goes.

The other alkaloids present in the leaves are mainly cinnamyl cocaine, isatropyl cocaine, and benzoyl ecgonine, all of which are much less active than cocaine. On hydrolysis these behave similarly to cocaine; for example, with cinnamyl cocaine the result is similar, except that cinnamic acid is formed in place of benzoic. Tannic acid is also present in small quantities.

Action

Local anæsthetic. Dilatation of the pupil. Stimulation of the central nervous system, beginning at the highest centres and followed by depression. General protoplasmic poison.

Local Action.—When cocaine is brought into direct contact with fine nerve-fibres or their endings, it paralyses them. On a mucous surface this effect can be produced by merely painting it with a solution of the drug. For example, a 5 per cent. solution of cocaine hydrochlorate applied to the tip of the tongue produces anæsthesia, beginning about a minute after the application and lasting for about fifteen minutes. All sensations, touch, heat, cold, and taste, with the exception of salt tastes, are paralysed. Local application to the conjunctiva results in complete anæsthesia, and most operations on the eye are performed now with the use of this anæsthetic alone. Similarly in the nasal cavities, throat, vagina, urethra, and rectum the local application of a cocaine solution produces temporary anæsthesia.

When applied to the human skin no effect is produced, because the drug is not absorbed. That the cutaneous nerve-endings are affected in the same way as those of the mucous surfaces can be shown in the frog, an animal whose skin absorbs readily, as, if one leg is placed in a strong solution of cocaine, the reflexes disappear rapidly. To produce anæsthesia of the skin in man the drug must be injected hypodermically, when the nerve-terminals, or more probably the finer nerve-bundles, are rendered insensible so far as the solution reaches them. In the extraction of teeth it is not sufficient merely to paint the gum with cocaine, but the drug must be injected, as it is only by this means that the nerve supplying the tooth can be reached.

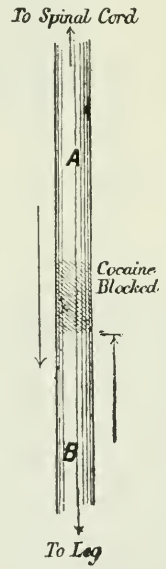


Fig. 36.—Diagram of the Sciatic Nerve of an Animal to Illustrate how Cocaine Paralyses Sensory Fibres before Motor.

A widespread anæsthesia may be induced by injecting cocaine into the spinal subdural canal. Complete paralysis quickly ensues below the point of injection whilst consciousness remains unimpaired; for example, 0.01 gram cocaine injected between the third and fourth lumbar vertebræ produces anæsthesia from the lower limbs up to the umbilicus. The anæsthesia begins in the extremities of the limbs three or four minutes after injection, the loss of sensation

spreads up, the last part to be affected being the region of the umbilicus. In these cases, patients are said to be able to appre ciate between heat and cold after sensation has disappeared, but this also ultimately goes. Recovery begins at the umbilicus and works downwards. The motor nerves are paralysed after the sensory and recover first, so that the patient may still be able to move his leg when sensation is lost.

Besides the local anæsthetic effect of cocaine, it has also a local vaso-constrictor action from direct stimulation of vaso-motor nerve-endings. After the constriction has passed off reaction occurs and the vessels are dilated more than usual. After absorption into the blood cocaine exerts no further anæsthetic action.

Two theories have been suggested to account for the action of cocaine on sensory nerve-endings:—(1) That it paralyses these endings much as curare or coniine paralyses the motor nerve-endings; and (2) that it is a general nerve-poison.

Cocaine certainly paralyses the trunk of a sensory nerve before the motor. This can be shown by exposing the sciatic nerve of a rabbit and applying a strong solution of cocaine to the centre of the exposed part (Fig. 36).

Electrical excitation at A will produce tetanus of the limb and general reflex movements of the animal. Excitation at B will produce tetanus, but no reflex movements. In other words, impulses can still pass downwards when they will not pass upwards, *i.e.* the sensory fibres are paralysed before the motor. The same fact is brought out by subdural injections into the cord, for when sensation is quite absent there is still some power of movement. Again, if cocaine is applied to the vagus nerve the inhibitory fibres to the heart are paralysed before the afferent fibres to the medulla (Fig. 37). Nevertheless, this may be the result of some physical difference, in the sheath of Schwaan, for example, which would not apply when the nerve-endings were exposed. There is not sufficient evidence for supposing that cocaine has a specific effect on sensory nerve-endings, and all the facts are explained by its known action as a general protoplasmic poison. The reason sensory nerve-endings are affected so readily is because of their exposed position.

Methods of producing Local Anæsthesia

1. **Subcutaneous Injection.**—The strength should not exceed 2 per cent., although the Pharmacopœia gives the official injection 5 per cent. Much advantage is obtained by combining cocaine or other local anæsthetic with adrenaline, because the anæsthesia lasts longer and the effect is increased since the alkaloid is kept locally by the intense vaso-constriction. The toxicity is also diminished since time is given for the adsorption of cocaine to the tissues. The adrenaline need not exceed 1 in 50,000. For painting on mucous membranes 10 per cent. cocaine may be employed.

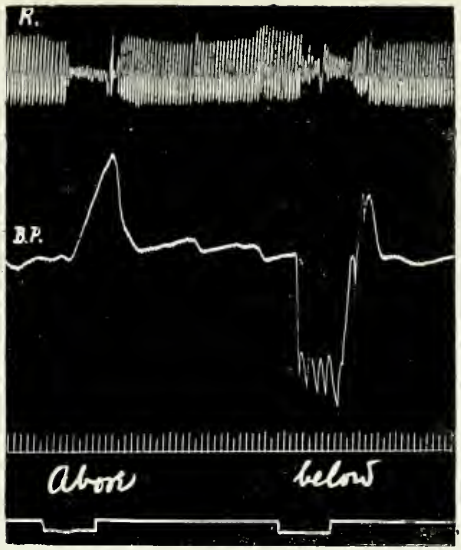


FIG. 37.—RABBIT. ETHER. RESPIRATION AND BLOOD-PRESSURE.

The left vagus is severed. 1 cm. of the right vagus has been painted with a 0.05 per cent. solution of cocaine. Stimulation above the painted spot is first shown, and later stimulation below. The cocaine blocks conduction downwards to the heart, but not upwards to the medulla. Time=secs.

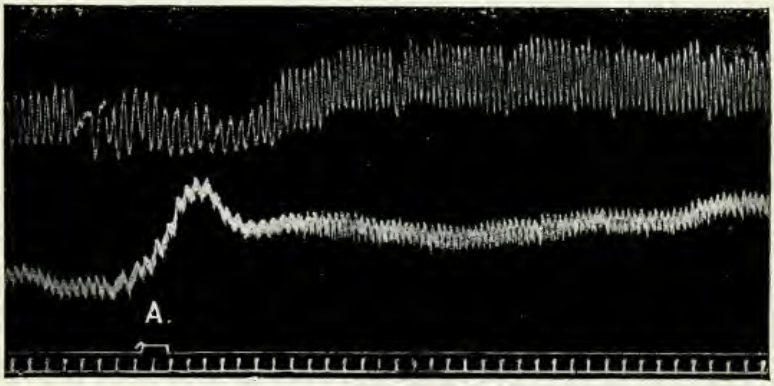


FIG. 38.—DOG. A.C.E., AND MORPHINE. RESPIRATION AND BLOOD-PRESSURE.

At A $\frac{1}{5}$ gr. cocaine was injected into the jugular vein. Note the stimulation of respiration and the rise in blood-pressure, both from medullary excitation. Time=secs.

To face p. 148.

2. **Regional Anæsthesia.**—Here the drug is injected close to the nerve trunk in the ramifications of which the operation is to take place.

3. **Infiltration Anæsthesia.**—Local anæsthesia occurs if water or salt solution is injected under the skin at a certain pressure so as to infiltrate the tissues. The injection is made at first into the skin in as many places as necessary until the area over the seat of incision is anæsthetised. Then the infiltration is continued deeper. In practice a very small quantity of cocaine is added to the saline to combat the pain of the infiltration pressure.

4. **Spinal Anæsthesia.**—This method will probably be little used in the future, because accidents, such as collapse, motor paralysis and paralysis of the bladder are too frequent.

5. **Sacral Anæsthesia.**—The drug is injected through a sacral foramen into the spinal canal. The anæsthesia, sometimes known as "riding breeches" anæsthesia, is evident in about a quarter of an hour. The anæsthesia affects the bladder, lower rectum, anus, external genitals, and the inner surface of the thigh.

Eye.—Cocaine when applied locally to the conjunctiva as a 2 per cent. solution produces vaso-constriction, dilatation of the pupil, and complete local anæsthesia. The effect is, therefore, peripheral in each case.

The dilatation of the pupil might be due to depression of the "nerve-endings" of the third nerve, but this is not the case, since stimulation of this nerve produces a normal constriction of the pupil. It might be due also to stimulation of the sympathetic nerve-endings, and this is regarded as the probable explanation, because, when the superior cervical ganglion is extirpated and the nerve-endings allowed sufficient time to degenerate, the local application of cocaine is said to produce no dilatation of the pupil. The dilatation is not maximal; atropine applied to a cocainised eye produces a yet wider dilatation, whilst pilocarpine will diminish it. Accommodation remains normal.

Effect on the Central Nervous System.—Cocaine produces a general excitation of the whole of the central nervous system. The effect begins in the highest centres, *i.e.* those centres which are last to develop, and slowly descends to the lower centres, affecting in sequence the motor-area, medulla, and cord. This excitation is followed by a depression having the same sequence, and hence it is possible to obtain simultaneous depression in one part of the central nervous system and stimulation in another. Its action is closely related to that of caffeine; but whereas the purine bodies affect mainly the "psychical areas," cocaine has apparently a greater affinity for lower centres, such as the motor area.

Small doses (1 gr.) administered to man produce exhilaration, loquacity, and hilarity, but the patient remains self-possessed, serene, and wakeful. His judgment and power of paying attention are increased and his reaction time is diminished. The drug is

therefore a direct nervous stimulant. The leaves are habitually chewed by some of the natives in South America to relieve fatigue and hunger and to produce exhilaration. Cocaine increases the work of muscle as measured by the ergograph, and in this respect it acts like caffeine: the action is especially decided during fatigue.

These effects are associated with a decided excitation of the motor cortex. There is a general tendency to movement which is of a perfectly co-ordinated character, and after large doses (3 gr.) tremors and some inco-ordination are seen. A small injection administered to a dog produces "circus movements," the animal continually rushes round and round the room in a circle, barking excitedly the while.

This stimulation of the cortex is very different from the effect of alcohol: it will be remembered that the latter drug acts by cutting off the controlling centres. With cocaine the effect is one of true stimulation, because (1) reflexes are increased, always a sign of stimulation—with alcohol they are diminished; (2) the reaction time is diminished—with alcohol it is increased after a very short stage of diminution; (3) the motor cortex is more excitable to electrical stimulation—in the case of alcohol it is less excitable; (4) there is a true stimulation of other parts of the brain, such as the medulla.

With large doses convulsions are produced resembling those of strychnine. These are mainly cortical in origin, because destruction of the superficial zone of Rolando abolishes them, although not completely; they are not entirely obliterated even after section of the medulla. Animals therefore in which the cerebral hemispheres are badly developed do not exhibit convulsions; thus they are not generally obtained in frogs, although the reflexes are considerably increased. The following table shows the relationship between the amount of cocaine necessary to produce convulsions and the degree of development of the cerebral hemispheres.

	Grams of Brain per kilo of Animal.	Dose of Cocaine per kilo necessary to produce Convulsions.
Rabbit	1	0.18
Guinea-pig	7	0.07
Pigeon	8	0.06
Dog	9	0.02
Ape	18	0.012

After toxic doses the temperature rises on account of some action on the heat-centres. The pyrexia does not occur in chloralised animals.

The medulla, like the other parts of the central nervous system, is stimulated. This is shown by (1) the effect on respiration, which is both quicker and deeper, and the action is still maintained after section of the vagi; (2) vaso-constriction, which is consider-

able—the blood-pressure, which is raised by the cocaine, falls immediately if the splanchnics are cut or the cord severed, showing that the stimulation is central (Fig. 38).

The **heart** is accelerated by moderate doses of cocaine and the vagal endings are slightly depressed. Some increase in rate occurs even when the vagi are paralysed by atropine, but it is stated that when the heart is artificially perfused with a solution of cocaine outside the body it becomes slower. The acceleration, according to this, results from some central stimulation and from depression of the vagal endings. The blood-pressure rises both from (1) vaso-constriction and (2) acceleration of the heart (Fig. 38).

Other Actions.—The peristaltic movements of the stomach and intestines are increased probably from a central effect, because if the cocaine is applied to living gut directly, all movements cease. It is believed that the drug has an action on the **semicircular canals**, since injections into pigeons produc peculiar pendulum motions or the head, lack of co-ordination, and rolling convulsions.

Cocaine is a general protoplasmic poison, that is to say, it destroys all forms of undifferentiated protoplasm. It stops the movements of cilia, spermatozoa and white blood-corpuscles. It paralyses and ultimately destroys all protoplasm, but it has a special affinity for nervous tissue. For example, if it is applied as a 5 per cent. solution directly to a piece of living gut, it paralyses the local nervous mechanism,

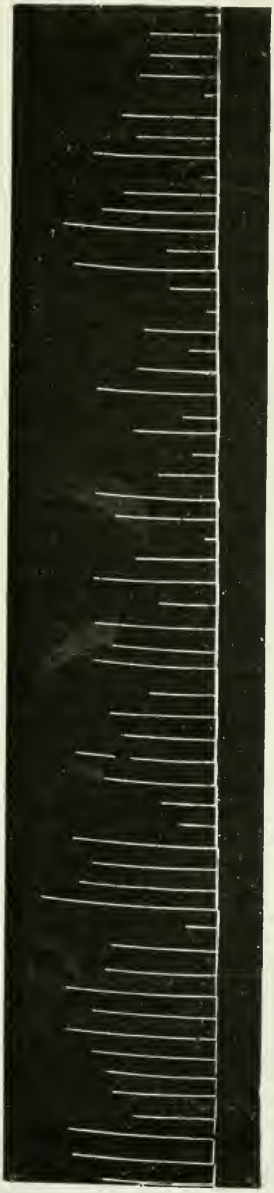


FIG. 39.—THE CONTRACTIONS OF A FROG'S GASTROCNEMIUS AS THE RESULT OF SIMPLE INDUCTION SHOCKS.

The frog had previously had a large dose of cocaine. The action is due to the gradual death of the muscle. Lead, emetics, ptomaines and other protoplasmic poisons produce the same effect. It is an index of the general toxicity of these bodies to living matter, and is of no direct therapeutical importance.

abolishes local reflexes and the power of the gut to move on a bolus before the muscle is attacked.

The **urine** is not much affected. The flow varies with the condition of the renal vessels. These are constricted at first and the urine is diminished somewhat, but later they dilate and the flow increases. About 70 per cent. of the injected cocaine can be detected in the urine. It is not possible to obtain tolerance to cocaine in animals; it may be possible in man, but there is, as yet, no evidence of its destruction.

Adsorption.—It has been pointed out already that strychnine injected with protein or milk loses some of its toxicity; apparently the alkaloid becomes adsorbed to colloids from which it is only slowly liberated. This effect is more important with cocaine. A lethal dose of cocaine injected into the leg of a cat or rabbit is without any poisonous effect if a tourniquet is placed on the leg above the seat of injection and kept there from a half to one hour. The toxicity is lost if the drug is kept for some time at the seat of application. Here again the cocaine appears to get adsorbed to the colloids, and its subsequent liberation is so slow as to exert no poisonous action. It may be for this reason that cocaine in dilute solution is so much less toxic than in strong solution.

With some people a cocaine **habit** may be formed in much the same way as with opium, hemp, or alcohol. Like other habits, once acquired it is not easily given up, the dose being rapidly increased, sometimes from 1 to 12 grs. It brings on insomnia, dyspepsia, emaciation, and convulsions.

The **symptoms** of a large dose of cocaine (10 grs.) commence with a stage of excitement, restlessness, and confusion. The patient cannot keep still, but is continually moving (excitation of the motor area). Occasionally there is vomiting and sometimes palpitation and fainting attacks. This condition is followed by a second stage of depression in which he likes to be left quiet and alone. The pupils are dilated, the respiration is accelerated, and the pulse is quicker, but never above 110. Reflexes are now increased and sometimes convulsive movements occur. This may be followed by collapse, death resulting from paralysis of the respiratory centre.

OTHER LOCAL ANÆSTHETICS

The ideal local anæsthetic should be soluble in water and the solution should be capable of sterilisation by boiling (cocaine is decomposed) : it should have a low toxicity and not cause inflammation or irritation after injection (cocaine is too toxic and too irritant).

Eucaine is a name given to two artificial alkaloids: α-eucaine, $C_{19}H_{27}NO_4$, and β-eucaine, $C_{15}H_{21}NO_2$. α-eucaine produces some irritation and pain before the stage of anæsthesia comes on, and is, therefore, not much used. β-eucaine is only one-fifth as toxic as

cocaine, and its anæsthetic action is more slowly developed and not so permanent. It does not constrict vessels nor dilate the pupil like cocaine, nor does it act well with adrenaline, but it is stable and solutions can be boiled. It is official as benzamine lactate.

Ethocaine (Novocaine), $NH_2 \cdot C_6H_4 \cdot COOC_2H_4 \cdot N(C_2H_5)_2 \cdot HCl$, is the most satisfactory of the recently introduced local anæsthetics. It is very soluble in water and its solutions are stable and can be boiled. Its toxicity is very low and it has no irritant action. For subcutaneous injections it is much superior to cocaine when mixed with adrenaline; without adrenaline its effect is too transient to be of much value.

Orthoform ($C_6H_3 \cdot OH \cdot COOCH_3 \cdot NH_2 \cdot$) is an insoluble powder used for dusting on raw surfaces and so producing relief from pain. The anodyne effect may last twelve hours or more. Doses of 1 to 3 grs. relieve the pain of cancer of the stomach. It is also used as an anodyne by insufflation in laryngeal tuberculosis.

Carbolic acid, when applied to the skin, gives rise to a feeling of burning, but at the same time produces partial anæsthesia.

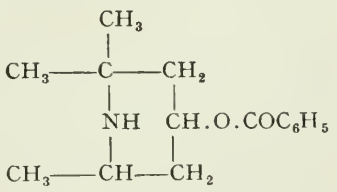
Quinine and Urea Hydrochloride. (*See* Quinine Anæsthesia.)

Atropine has a local anæsthetic action in a mild degree. To produce an effect on the skin the drug must either be rubbed in or applied for a long time in the form of a plaster.

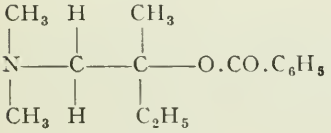
Aconitine and **Veratrine**, rubbed into the skin, stimulate the sensory nerve-endings and give rise to a feeling of tingling and warmth. The stimulation passes into depression, and numbness is the final effect.

Stovaine, like novocaine, is an excellent local anæsthetic. It has the disadvantage that it is more irritant than novocaine, and dilates blood-vessels so that it acts poorly with adrenaline.

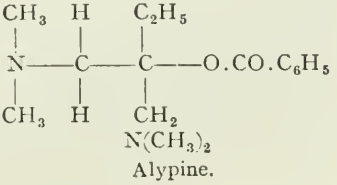
The group $\begin{array}{|}\hline N-C-C-C-O\cdot CO\cdot C_6H_5 \\ \hline\end{array}$ forms an integral part of the local anæsthetics cocaine and benzamine, whilst other synthetic local anæsthetics contain the closely related group $\begin{array}{|}\hline N-C-C-O\cdot CO\cdot C_6H_5. \\ \hline\end{array}$ They are interesting as they show how one type of structure may sometimes determine the pharmacological action.



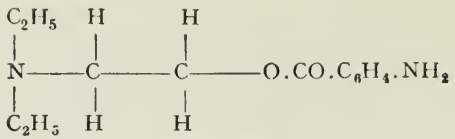
Benzamine or Eucaine.



Stovaine.



Alypine.



Novocaine.

HYDROCYANIC ACID

Acidum hydrocyanicum dilutum is an aqueous solution containing 2 per cent. HCN, obtained by distilling potassium ferrocyanide with dilute sulphuric acid. The official solution loses its strength through careless storage either by volatilisation or by decomposition, thus :—

$$HCN + 2H_2O = H.COO.NH_4$$

Ammonium Formate.

This transformation, ordinarily slow, is much hastened by light. Hydrocyanic acid may be regarded as an isocyanide HN=C and is closely related to the organic isocyanides.

Amygdala Amara.—Bitter almonds, the ripe seeds of *Prunus amygdalus*. The seeds contain amygdalin, a crystalline glucoside which is decomposed in the presence of water by an enzyme emulsin.

$$\underset{\text{Amygdalin.}}{C_{20}H_{27}NO_{11}} + \underset{\text{Water.}}{2H_2O} = \underset{\text{Dextrose.}}{2C_6H_{12}O_6} + \underset{\substack{\text{Benzaldehyde}\\ \text{(oil of bitter}\\ \text{almonds).}}}{C_6H_5.CHO} + \underset{\substack{\text{Hydrocyanic}\\ \text{acid.}}}{HCN}$$

Bitter almonds contain about 40 per cent. of fixed oil, about 0.9 per cent. of volatile oil, and they yield also about 0.25 per cent. hydrocyanic acid.

Pruni Virginianæ Cortex (wild black cherry).—The bark contains a glucoside, and when it is macerated with water it yields benzaldehyde, $C_6H_5.CHO$, and from 0.15 to 0.2 per cent. HCN. The glucoside is evidently allied to amygdalin, and the change is brought about by a ferment similar to emulsin. The bark also contains a bitter crystalline glucoside and 3 or 4 per cent. of tannin, together with some resin, starch, and fatty matters.

Laurocerasi Folia (cherry laurel leaves).—The chief constituent is "laurocerasin," a glucoside related to amygdalin. It is decomposed in the presence of water by emulsin into benzaldehyde, hydrocyanic acid, and glucose. The fresh leaves yield about 0.1 per cent. HCN.

Hydrocyanic or prussic acid and its salts are very widely distributed in nature : they occur naturally, though in minute quantities, in some plants and animals, and sulphocyanide is a normal constituent of human saliva. Prussic acid is evolved during the oxidation of albumen.

Action.

External.—Hydrocyanic acid is a general protoplasmic poison, and the activity of both animal and vegetable tissues is diminished in the presence of very minute amounts. When it is applied directly to an isolated nerve-muscle preparation both the nervous and muscular tissues rapidly lose their irritability and are paralysed synchronously, so that excitation of the nerve at any one moment produces exactly the same effect as exciting the muscle directly. The movements of infusoria, spermatozoa, and cilia are all arrested. It inhibits fermentations and putrefaction, although, curiously enough, some species of bacilli are but little influenced by its presence, a fact which we cannot explain at present.

Hydrocyanic acid, when applied to a mucous membrane or to some surface from which it can be absorbed, paralyses the peripheral sensory mechanism like most other general protoplasmic poisons. For example, if the skin of a frog's leg is painted with a 3 per cent. solution, no reflex response is elicited by pinching the skin of this leg. In this case the sensory nerves are paralysed, not necessarily on account of any specific effect of the acid upon them, but because the sensory fibres are much more exposed than the motor.

Absorption.—When hydrocyanic acid is administered internally in fairly concentrated doses it produces a sensation of burning in the mouth, and reflex salivation; this is followed by numbness in the mouth and throat. In the stomach also the fine sensory nerve-fibrils are depressed, so that hydrocyanic acid is frequently used in the treatment of dyspepsia, both on account of its relieving gastric pain and for its antiseptic properties.

This drug is absorbed with extraordinary rapidity: if a little of the strong acid is placed upon an animal's tongue it can be detected in the blood thirty or forty seconds later. The inhalation of the anhydrous acid for one second kills a guinea-pig, and accidental inhalations of the dilute acid of the Pharmacopœia (2 per cent.) give rise to poisonous symptoms in man.

Nervous System.—Hydrocyanic acid first excites and subsequently depresses the central nervous system. The effects of the stimulant action are particularly noticeable on the medulla, and hence the vomiting, vaso-constriction, cardiac slowing, and acceleration of the respiration due to the effect of the drug on the vaso-motor, vagal, and respiratory centres respectively. These effects are short in duration and are followed by depression.

The blood-pressure rises at first, on account of the vaso-constriction (Fig. 40); this constriction is due to a direct action of the drug on the centre, since it is not obtained if, previously to the administration of the drug, the cord is severed high up. The blood-pressure rises in spite of cardiac slowing, and if the slowing is prevented, as it is when the medullary influences are cut off by section of the vagi, the pressure rises even higher. The rise is of very short duration, and is quickly succeeded by a fall due to vaso-dilatation.

which is the direct outcome of medullary depression. The stimulant effect on the medulla is best indicated by the respiration, which becomes quicker and very much deeper; but in spite of this the absorption of oxygen and the elimination of carbonic acid are actually diminished (Fig. 41). Depression follows the stimulation and the breathing becomes slower and shallower: death ensues from asphyxia.

Very large doses of hydrocyanic acid directly depress the heart, as can be seen by perfusing very dilute solutions of the drug through an isolated mammalian heart. After lethal doses, not only is the central nervous system paralysed but the automatic power of contraction of the heart is also destroyed, so that in these cases artificial respiration does not prolong life.

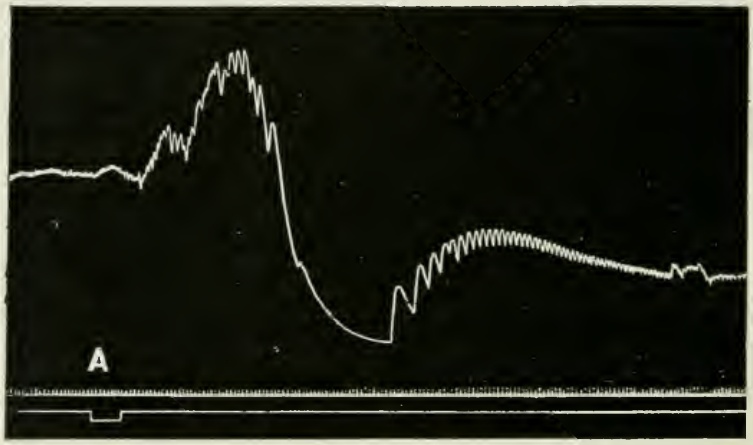


FIG. 40.—CAT. A.C.E. BLOOD-PRESSURE.

At A, 3 m. of dilute HCN were injected into a vein. There is an immediate rise of blood-pressure and slowing of the heart-beat due to stimulation of the medulla. The subsequent effect is due in a small degree to paralysis of the medulla, but mainly to the direct toxic effect of HCN on cardiac muscle. Time = secs.

Metabolism.—Hydrocyanic acid is rapidly destroyed by living matter, but whilst it is in the circulation it profoundly affects metabolism, so that the tissues gradually lose their power of absorbing oxygen from the blood: deficiency of oxidation must ensue in consequence, and here, as in all such conditions, the blood is found to contain various abnormal substances, and not uncommonly an excess of sugar and lactic acid.

It was formerly believed that hydrocyanic acid produced its effect by fixing the oxygen more firmly to the hæmoglobin, so that oxidation of the tissues became impossible. Hydrocyanic acid has, however, little or no effect on the blood when it is administered in non-lethal doses; and if a little blood is drawn off from an animal which has had a large but non-lethal dose of the drug, the oxygen

can be pumped off from it as readily as from normal blood. The bright red colour of the blood, which is characteristic of animals that have died from poisoning by hydrocyanic acid, is due to the tissues which do not reduce the oxyhæmoglobin.

Nevertheless, if hydrocyanic acid is added to drawn blood a change is produced. This may be shown, in the first place, by adding to a little drawn blood containing hydrocyanic acid some hydrogen peroxide, when there is no effervescence, whilst with normal blood a copious effervescence of oxygen is immediately observed. The hydrocyanic acid enters into chemical combination with the hæmatin, and forms a compound having a bright red colour: this body, cyanhæmatin, sometimes also termed cyanmethæmoglobin, although globulin does not enter into its composition, is easily formed by adding a little HCN to an alkaline solution of hæmatin, or to a solution of methæmoglobin. The reaction forms a sensitive test for the presence of HCN, and may be performed as follows:—A little methæmoglobin is prepared by adding some amyl nitrite or potassium chlorate to blood; this is sucked up by bibulous paper, which is then allowed to dry. The presence of a trace of HCN on the bibulous paper is marked by a change of colour from dark brown to bright red. Cyanhæmatin has an absorption spectrum between the D and the F lines very similar to the spectrum of reduced hæmoglobin.

Hydrocyanic acid is partially destroyed in the tissues and is partly changed to sulphocyanides, which are excreted in the urine.

Symptoms.—The symptoms arising after a large dose, half an ounce, are of very short duration. Almost immediately the respiration becomes spasmodic, there is a gasping scream, a few convulsive movements, and then unconsciousness. Death results from paralysis of the central nervous system, but artificial respiration is of no use for prolonging life since the poison also kills the heart. Post-mortem, the blood is a bright red colour. When smaller doses have been given there is often a feeling of numbness in the mouth and throat, soon followed by headache, vomiting, and confusion of thought. The breathing is deep and gasping in character, and the patient complains of great muscular weakness; unconsciousness supervenes, and usually a few convulsive movements precede death, which is produced as before by paralysis of the nerve-centres.

It is difficult in these cases of poisoning to know what remedial measures to adopt. The drug is so rapidly absorbed that chemical antagonists are too late. Medullary stimulants such as strychnine are generally employed, and in late years sodium hyposulphite has given some promising results. Sodium hyposulphite acts by forming the non-poisonous sulphocyanide and is effective after absorption. From 2 to 4 drachms dissolved in water should be administered as a hypodermic injection.

QUININE ANÆSTHESIA

Quinine has been used as a local anæsthetic combined with urea, which increases its solubility and enables it the better to penetrate tissues, but the new compound is weaker, and must be used in twice the strength which would be required for quinine. The quinine derivatives differ from cocaine and its allies in that they are more destructive to tissues other than nerve; that is, they are less specific for nerve.

The necessary strengths of the quinine derivatives to produce local anæsthesia of the rabbit's cornea have been estimated as follows:

STRENGTHS OF QUININE DERIVATIVES PRODUCING CORNEAL ANÆSTHESIA

Quinine HCl	1 in 60
Cocaine HCl	1 in 50
Hydroquinine HCl	1 in 100
Ethyl hydrocupreine NCl	1 in 100
Isopropylhydrocupreine HCl	1 in 800
Isoamylhydrocupreine HCl	1 in 1,200
Eucuprinotoxine (Isomeric with the last)	1 in 2,000

With all these salts the latent period before anæsthesia occurs is longer, by about four times, than that of cocaine, but the anæsthesia is prolonged, lasting one hour or more.

The nature of this anæsthesia is entir'y different from that produced by cocaine, stovaine, novocaine, and the like. The latter drugs exert a selective action on nerve fibrils, and when they are placed under the skin they paralyse all nerve fibrils with which they come in contact, leaving other tissues relatively unaffected. The quinine derivatives, though they may be twenty or more times as powerful as cocaine on the rabbit's cornea, have little or no selective action for nerve fibrils. When placed under the skin in concentrations which will not paralyse sensory nerve fibrils they nevertheless produce anæsthesia. This clearly suggests that they may *affect the sensory nerve-endings.*

MATERIA MEDICA

Acidum Hydrocyanicum Dilutum.—2 per cent. **Dose, 2 to 5 m.** (12 to 30 centimils).

PREPARATION

Tinctura Chloroformi et Morphinæ Composita.—½ m. of acidum hydrocyanicum dilutum in 10 m.

Dose, 5 to 15 m.

Pruni Virginianæ Cortex.

PREPARATIONS

1. Syrupus Pruni Virginianæ.
   Dose, ½ to 1 dr. (2 to 4 mils).
2. Tinctura Pruni Virginianæ.
   Dose, ½ to 1 dr. (2 to 4 mils).

Laurocerasi Folia.

PREPARATION

Aqua Laurocerasi. Standardised to 0.1 per cent. of hydrocyanic acid.

Dose, ½ to 2 drs. (2 to 8 mils).

Hydrocyanic acid is also present in bitter almonds.

Cocaina.

PREPARATION

Unguentum Cocainæ.—4 per cent.

Cocainæ Hydrochloridum. Dose, $\frac{1}{10}$ to $\frac{1}{4}$ gr. (6 to 16 mgrms.).

Subcutaneously 1 per cent., eye 2 per cent., for painting on mucous membrane 10 per cent. Cocaine is best used with adrenaline about 1 in 50,000.

PREPARATIONS

1. Injectio Cocainæ Hypodermica.—5 per cent. Contains some salicylic acid to preserve the solution.
   Dose, 5 to 10 m. (3 to 6 decimils) subcutaneously.
2. Lamella Cocainæ.—Each containing cocaine hydrochloride $\frac{1}{50}$ gr. (1.3 mgrms.).
3. Trochiscus Krameriæ et Cocainæ.—Each contains cocaine hydrochloride $\frac{1}{20}$ gr.

Benzaminæ Lactas. Dose, $\frac{1}{8}$ to ½ gr. (8 to 30 mgrms.).

For the eye 2 per cent., urethra, 2 per cent., nose and throat 5 per cent.

Novocaine Ethocaine, not official.

For subcutaneous injection, 2 per cent.

Orthoformum, not official. Dose, 8 to 15 grs. (0.5 to 1 grm.).

CHAPTER X

GROUP OF DIURETICS

The Purine Derivatives, Scoparium, Uva Ursi

Diuretics are medicines used to increase the flow of urine. Some of them only act in diseased conditions; digitalis, for example, is diuretic only when there is venous congestion of the kidneys. It acts by removing this state of affairs, and so allows arterial blood to pass once more through the renal vessels, and hence the increased flow of urine.

Cold acts as an excellent diuretic by checking the secretion of the skin. Water increases the flow of urine without sensibly affecting the elimination of urea and uric acid, though the chlorides seem to be increased.

The diuretics can be classified as follows:—

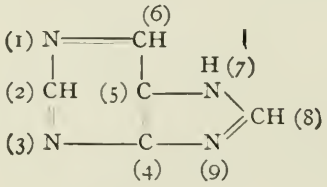
(1) Salines.

(2) Drugs which dilate the renal vessels without materially lowering the blood-pressure: caffeine and its allies; urea; essential oils; scoparium.

(3) The digitalis group, which is only diuretic in certain pathological conditions, and does not increase the urine of the normal man.

THE PURINE DERIVATIVES

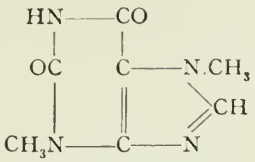
E. Fischer applied the term purine to a nucleus that he prepared



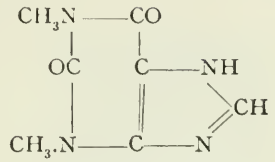
Purine.

and from which derivatives can be produced by direct addition or substitution of atoms or radicles. The names and formulæ of the

most important members of the group employed in medicine are as follows :—

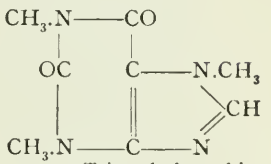


3. 7. Dimethylxanthine Theobromine.



1. 3. Dimethylxanthine Theophylline (Theocin).

The purine derivatives occur in the animal body, combined with albumen in the form of nucleo-protein, and during normal metabolism a small amount is set free and constitutes the " endogenous " purines of the excreta as opposed to the exogenous which occur in all flesh, and meat extracts, and in some vegetables. It should be noted that the endogenous purines in animals and plants are non-methylated.



1. 3. 7. Trimethylxanthine Caffeine.

Caffeine is an alkaloid obtained most readily from tea, which contains anything from 2.5 to 4.5 per cent. Many other plants which are employed in all regions of the globe as decoctions or infusions for drinking purposes have been found on analysis to contain caffeine or one of the allied alkaloids. Thus we have coffee from Arabia containing caffeine, cocoa from South America containing theobromine, kola from Central Africa containing both caffeine and theobromine, and several others.

Action

Caffeine exerts three important actions when taken into the animal body :—

(1) *It excites the central nervous system.*

(2) *It has an action on all muscle-fibre—striped, plain, and cardiac.*

(3) *It is a diuretic.*

The drug is absorbed very easily, and exerts little or no action on the alimentary canal.

Central Nervous System.—The action of small doses of caffeine is mainly on that part of the brain connected with psychical functions, and it seems to act here in much the same way as strychnine acts on the cord. It facilitates the perception of sensory stimuli as well as the association of ideas, and if we regard our object consciousness as the sum total of impulses perceived at any one moment, then consciousness is increased. All our sensory impressions normally are connected with others, and habits of association are formed; caffeine strengthens these bonds and the association of ideas is

brought about more readily. These effects will induce a condition of wakefulness; and drowsiness or fatigue if present—conditions resulting from a diminished consciousness—will disappear. Mental activity is increased, the interpretation of all sensory impressions is more perfect and correct, and thought is clearer and quicker than in the normal state. Caffeine decidedly facilitates the performance of all forms of physical work. Experiments have been made with the ergograph in which it has been shown conclusively that caffeine increases the amount of muscular work which a normal man can perform, and that after small doses this is not followed by a reaction as in the case of strychnine. Caffeine in large doses may be followed after the stimulation stage by a reaction during which work is diminished. It is by no means certain that the whole of this effect is nervous: it has also been explained by the action of caffeine peripherally on muscle, and will be referred to again. But as fatigue shows itself first on the centre, it is probable that the action of caffeine in diminishing fatigue is mainly central.

Larger doses of caffeine give rise to some confusion of thought, associated with subjective affections of the sense-organs, such as flashes of light before the eyes and singing in the ears. The patient, whose reflexes are always increased at this stage, becomes very excitable and restless; he is tremulous in his actions, and often exhibits spasmodic movements of the limbs: the condition may terminate in tonic convulsions. The increased movement is responsible for a small rise of temperature.

Caffeine is, therefore, a true cerebral excitant; its action begins upon the psychical areas, and with small doses this is the only part of the cerebrum appreciably affected. Next the motor area is stimulated and restlessness ensues; and, lastly, the cord is affected as shown by the convulsions.

The convulsions are spinal in origin; this may be readily shown in the frog, for they are abolished as the cord is destroyed from before backwards; indeed, this animal shows no symptoms which cannot be ascribed to an action on the spinal cord. In this connexion it must be remembered how little the frog's brain is differentiated, and also that as the cerebral hemispheres become more and more complex in the scale of evolution, so the action of caffeine resembles more and more that seen in man, and less and less does it augment the spinal reflex excitability. Caffeine has a selective action on the higher centres of the cerebrum; the greater the development of this organ in an animal the smaller becomes the dose of caffeine relatively necessary to produce an effect.

Before leaving the action of caffeine on the central nervous system its effect on the medulla must be considered briefly. Even small doses of caffeine excite the medulla, and so there is general vaso-constriction and decided stimulation of respiration. The cardio-inhibitory centre, no doubt, is also stimulated, but this effect is of no significance, since the peripheral action of caffeine

on the cardiac muscle completely overshadows this medullary action.

Muscular Tissue.—Caffeine has a specific action on all forms of muscle-tissue, striped, plain, and cardiac. It is convenient at first to observe the action on the *striped muscle* of the frog. If a small injection of caffeine is made into the lymph-sac of a frog which has the vessels of one hind-leg ligatured, and if after an appropriate interval the two gastrocnemii are compared, the one to which the caffeine has obtained access will be affected in such a way that with a successive series of stimuli it is capable of performing more work than its fellow. By work here is meant the total height to which the muscle, provided with a suitable stimulus, can raise a given weight. The muscle is directly stimulated and it will contract to weaker stimuli, or against a greater load to the same height as its fellow. Similar effects have been induced in mammals, and as the result of experiments in man, the work obtained from electrical excitation of a living muscle is found to be increased by the administration of caffeine.

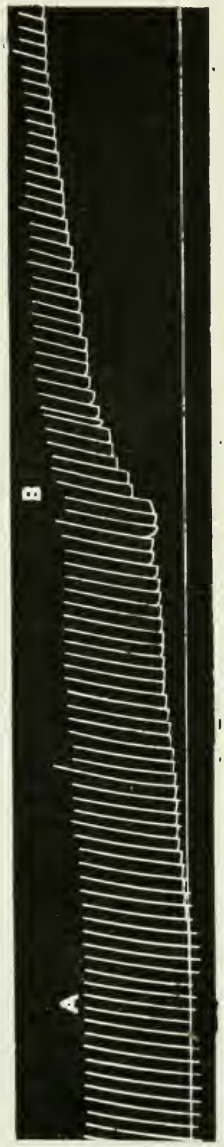


FIG. 42.—FROG'S GASTROCNEMIUS. SINGLE INDUCTION SHOCKS ON THE STATIONARY DRUM.
At A a 0.3 per cent. solution of caffeine was applied, and at B a 2 per cent. solution. The therapeutic effect of caffeine on muscle is not shown here, but only the poisonous action (rigor).

Larger doses of caffeine produce a profound change in the muscle-protoplasm. This change is shown by the muscle becoming contracted, hard, opaque, and acid, and passing into a condition of rigor. If a little muscle-juice is allowed to pass over a glass plate and meet a solution of caffeine the coagulation can be observed under the microscope, and the myosinogen is apparently converted into myosin: it is obviously a true rigor, since the ferment inducing the post-mortem change is increased by caffeine. Excitation of a frog's muscle after such big doses shows a gradually increasing amount of contracture (Fig. 42). Similar changes can be produced in mammalia, though only with difficulty.

Therefore, the problem as to how caffeine diminishes fatigue and increases the amount of work men are capable of performing becomes complex. There can be little doubt that both the central and peripheral effects exert some beneficial influence, but it is probable that the central action is the more important; and this for two reasons: first, because we know that fatigue is principally central in origin, and so it could hardly be influenced by a drug which acts on muscle; and secondly, because other drugs which directly excite the cerebrum and psychical centres, such, for example, as cocaine, have a similar effect in diminishing fatigue. But there are no drugs that do this to the same extent as caffeine.

Caffeine has also some action on *plain muscle.* This effect has been properly investigated only for the plain muscle of the blood-vessels. If a dilute solution of caffeine is perfused through any blood-vessels in the body they invariably dilate to a very decided degree, and the outflow of the perfusing fluid is increased. This action of caffeine must be one on the muscles and not on the nerve-endings, because the pulmonary vessels which contain no nerve-fibres dilate to an equal extent with the systemic vessels.

On Cardiac Muscle and on the Circulation.—The most characteristic feature of the action of caffeine on the heart is the acceleration of the rhythm, and it is brought about by a diminished pause in diastole. It is independent of the inhibitory apparatus of the heart, for it occurs when the vagal terminals have been paralysed by atropine; and as the acceleration is still produced in the isolated heart, it must be ascribed to an effect either on heart-muscle or to stimulation of the terminations of the accelerator nerves.

If the acceleration is due to stimulation of the nerve-terminations there should also be, in all probability, a great augmentation in the force of the beat; but this is not the case: moreover, it is possible to paralyse completely these nerve-terminals by means of apocodeine —a drug which has been referred to already under Opium—and after such paralysis caffeine still produces acceleration. The increased rate of beat must be attributed, therefore, to an action on the muscular apparatus which gives the rhythm to the lower parts of the heart, and which we may term the excito-motor apparatus, and which corresponds with nodal tissue and the bundle of His. The force of contraction is slightly increased after moderate doses of caffeine. It is quite a small effect, and is, no doubt, due to the extension of the action to the ordinary musculature of the heart (Fig. 43). The total effect of therapeutic doses of this drug is to increase the rate of the heart and, to a small extent, the force of contraction, so increasing the output of blood per minute.

Larger doses of caffeine produce a shortening of the movements commencing in the auricle and spreading to the ventricle. This, no doubt, is due partly to the cardiac acceleration, and may be considered a secondary effect of the increased irritability of the

excito-motor area, but it is due also to the extension of action of the drug to the ordinary muscle of the auricle and ventricle.

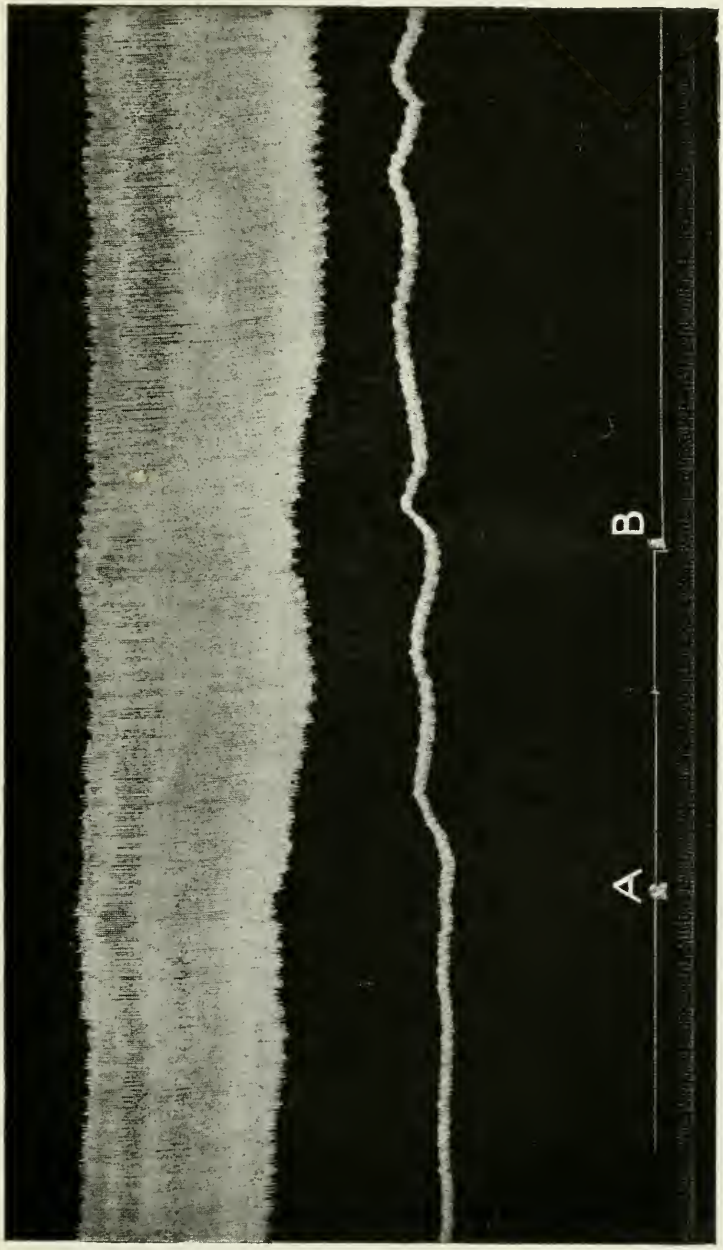


FIG. 43.—CAT. URETHANE. CARDIOMETER AND BLOOD-PRESSURE.

The upper tracing records the volume of the heart; as the heart fills the lever rises, and during systole it falls. At A 1 c.c. 0.5 per cent. caffeine, H.Cl, was injected into the jugular vein. At B 2 c.c. were injected. Cardiac systole is augmented, the heart beats more quickly (not seen on the tracing) and B P. rises. The rise in B P. is due (i) to increased cardiac output, and (ii) to vaso-constriction. Time = secs.

This stage is followed by the third stage of auriculo-ventricular arhythmia terminating in fibrillary contractions of the auricle, and finally of the ventricle: it is the result of ventricular irritability being so greatly increased as to give rise to an idioventricular rhythm, the latter being characteristic of the stimulant action on cardiac muscle. Thus the action of caffeine consists of a descending stimulation, which begins in the excito-motor area at the junction of the auricle and great veins, and extends into the auricles and finally to the ventricles.

The action of caffeine on the blood-pressure is the resultant of all these various effects. The increased output from the heart and the stimulation of the vaso-motor centre will tend to raise the blood-pressure, whilst the peripheral action on the vessels tends towards dilatation and, therefore, to a fall of pressure. The initial effect of caffeine is invariably to raise blood-pressure, both as the result of vaso-constriction which at first overshadows the peripheral tendency of the vessels, and the increased cardiac output. After a varying period, generally about twenty minutes when the drug is administered by the mouth, the peripheral effect of the drug comes into play and the vessels dilate. The blood-pressure will then fall a little, but never to any great extent, and with medicinal doses, probably not much if at all below normal, the augmented output from the heart being sufficient to counterbalance the dilatation.

One point worthy of especial attention is the action of caffeine upon the pulmonary, cerebral, and coronary vessels; these contain no nerve-supply of practical significance, hence the whole action of caffeine is exerted on them peripherally, so that they dilate no matter what the condition of the systemic vessels. Caffeine should therefore improve the nutrition of the lungs, brain, and heart.

Kidney.—Caffeine and its allies form a very important group of diuretics. They all decidedly increase the secretion of the water of the urine. The urine is generally of a lower specific gravity than normal, since it contains per c.c. less salt and urea; but the total excretion of solids, both as regards nitrogenous elements, urea and uric acid, and salts, is increased. This is important, since caffeine and its allies are often prescribed to remove the fluid of dropsy. Dropsical fluid contains salts in the same proportion in which they exist in blood (0.9 per cent.), so that if water only were excreted the salts would rapidly reabsorb the water they required to render their solutions isotonic and the dropsy would rapidly return.

Two hypotheses have been suggested to account for the diuresis. The one regards the effect as entirely due to alterations in the vascular conditions of the kidney, and the other supposes a specific effect of these purine bodies on the renal epithelium.

If an injection of caffeine be made under the skin of an animal in which the blood-pressure, the kidney volume, and the flow of

urine are being recorded, a very definite result is obtained. At first the blood-pressure rises both from the augmented cardiac output and the vaso-constriction originating in the centre; the renal vessels gradually constrict, and hence the kidney volume diminishes and the secretion of urine during this stage invariably runs parallel to the kidney volume, so that the flow rapidly becomes less. In from ten minutes to half an hour the picture gradually changes. The blood-pressure falls a little, although the height is still slightly above normal, the renal vessels begin to expand and, having assumed a condition of very considerable dilatation, remain in that state for a time varying from one to three hours; and now the urine begins to flow more freely, and reaches its maximum when the dilatation of the kidney is greatest; the parallelism between the renal vessels and the flow of urine is generally constant, but not always.

This picture is true in man when a dose of caffeine is taken by the mouth, except that the effect is not so suddenly produced and lasts longer.

The initial constriction of renal vessels is produced by central stimulation. It does not occur if the nerves to the kidney are all severed, in which case vaso-dilatation is present throughout, and is associated with an increased flow of urine. In order to eliminate this initial vaso-constriction and so increase the diuretic power of caffeine, it has been suggested that it might be given along with another drug, such as chloral, which depresses the centre. Such a mixture will increase the flow of urine immediately, but it is open to obvious objections. A similar effect may be produced by other purine derivatives, such as theobromine, which, though acting like caffeine on the kidney, has little or no exciting action on the vaso-motor centre.

We have now to decide whether the vaso-dilatation is the cause or the effect of the augmented secretion of urine. Those who assert that caffeine has a specific action on renal epithelium generally regard the vaso-dilatation as the result of renal activity. This we have already shown is not the case: the vaso-dilatation is the result of the effect of caffeine on the muscle-substance of the arterioles, and it is produced in every organ of the body without exception. Whenever there is an increased flow of urine from caffeine we invariably find that there is some corresponding vascular effect; the mere presence of caffeine in the circulation ensures this. We have seen already that the central action of caffeine tends to constrict vessels, and the peripheral action to dilate them. So that those vessels which are innervated best will perhaps remain constricted whilst the others are dilated. Let us take one example to show the difficulties that the renal circulation presents. Supposing the efferent vessels from the glomeruli are well innervated, then they become constricted, the kidney volume dilates, but the amount of blood passing through the renal vessels per minute does not increase and may diminish.

According to the filtration hypothesis, the flow of urine depends both on the degree of dilatation of the renal vessels and the amount of blood passing through them per minute. Blood-pressure is, therefore, a factor which cannot be neglected. A high blood-pressure is of little diuretic value if the renal vessels are constricted, and similarly a low blood-pressure with a great dilatation of the renal vessels will have little effect on the urine. Caffeine dilates the vessels, and yet the blood-pressure does not fall. In further support of this hypothesis it may be pointed out that the various purine derivatives are diuretic just in proportion as they dilate vessels.

In support of the vital theory, it has been pointed out (1) that diuresis can be produced by urea, sodium sulphate, and other substances, without increasing the rate of blood-flow ; (2) that injections of urea and sodium sulphate may produce a urine of lower concentration than that of the serum ; (3) that diuresis goes hand in hand with an increased absorption of oxygen by the kidneys, an effect which is regarded as evidence of increased activity of the renal cells. The increased oxygen absorption is independent of the blood-flow and of the concentration of the urine.

Ringer's solution causes diuresis without altering gaseous metabolism ; diuresis must in this instance be a filtration. Sodium sulphate causes diuresis and increases gaseous metabolism, so that this salt increases the work of the kidney and may be regarded as a true stimulant to renal cells.

Respiration and Metabolism.—Caffeine is a very decided stimulant to the respiratory centre ; both the number and the depth of the respirations are increased. In correlation with this fact. we find that the absorption of oxygen and the excretion of carbonic acid are also augmented. Metabolism is more active, though not to any marked degree, for the excretion of urea and salts in the urine is not much influenced.

Excretion.—A considerable portion of the caffeine administered is excreted in the urine as monomethyl xanthine and dimethyl xanthine, part is excreted unchanged, while the fate of the greater part is not certainly known.

Differences in Action between the Different Members.—All the purine bodies exert two marked actions :—

(1) They increase the sensibility of the central nervous system to external stimuli; as the dose is increased this passes into tetanus, and may ultimately end in paralysis.

(2) They act on the muscles, first facilitating their contraction, but producing rigor when the dose is large.

The relative degree of these two actions varies in the different members. The action of theobromine is mainly on the muscles, and it has little or no effect on the central nervous system; and parallel with the effect on the muscles is the diuretic action, the two effects always increasing and diminishing together.

Theophylline is a better diuretic than either caffeine or theo-

bromine, but it excites the central nervous system even more than caffeine.

The nervous action is said to depend upon the presence of nitrogen in the molecule, and is a characteristic action of ammonia and its salts, whilst the muscular action is peculiar to the purine ring. Purine exhibits both actions. The introduction of oxygen or alkyl groups alters the degree of the two effects, both absolutely and relatively, in an extremely irregular fashion. Possibly these irregularities are due to the differences in solubility and the rate at which the drugs penetrate to the muscle-fibres and nerve-cells, and it is probable that for some such reason 7 oxy-purine produces no muscular rigor and 2 oxy-purine no tetanus, whereas with the 1 : 6 dimethyl derivative of the first and 1 : 3 dimethyl derivative of the second the missing action is manifested: the first two substances are insoluble in water and only slightly soluble in aqueous sodium carbonate, whereas the second two dissolve readily in water.

SCOPARIUM

Scoparii Cacumina (broom-tops) are obtained from *Cytisus scoparius*. Their chief constituent is the liquid volatile alkaloid sparteine ($C_{15}H_{26}N_2$), but they also contain an indifferent substance scoparin, which contains the phloroglucinol complex. Many writers have ascribed the diuretic properties of scoparium to this substance. It has, however, no action on the flow of urine.

It is customary when a diuretic effect is required to give the drug in the form of an infusion, as the active principles have not proved of much value. In healthy men it seems clear that scoparium is not a diuretic, although in certain diseased conditions the urine is increased.

BUCHU

Buchu leaves are obtained from *Barosma betulina*. They should yield from 1 to 2 per cent. of volatile oil, containing about 30 per cent. of crystalline diosphenol, $C_{10}H_{16}O_2$. The oil also contains menthone, a hydrocarbon resin.

Buchu has the ordinary properties of the volatile oils, and, like them, during its excretion by the kidneys induces local dilatation with corresponding diuresis.

UVÆ URSI FOLIA

Bearberry leaves are obtained from *Arctostaphylus uva-ursi*. They contain crystalline glucosides arbutin and methyl-arbutin, a small quantity of some other glucosides, a crystalline resinous body ursone, gallic acid, quercitin, and 6 or 7 per cent. of tannin.

When given by the mouth arbutin is partly decomposed, and one of the products of its hydrolysis is hydroquinone,

but most of the arbutin is absorbed and excreted unchanged by the kidneys.

It is decidedly diuretic in its action, this being, no doubt, the result of the excretion of the drug by the kidney ; it is employed also as a mild antiseptic and stimulant to the genito-urinary tract.

The administration of arbutin produces a greenish-brown urine, which darkens on standing; this is due to the hydroquinone, which quickly undergoes further oxidation like other members of the benzene series.

Uva ursi is astringent on account of the tannin it contains ; large doses produce gastro-intestinal symptoms, but death from the drug is unknown.

Allantoin $C_4H_6O_3N_4$ is a diureide of glyoxylic acid and is prepared by the oxidation of uric acid. It occurs in the allantois and in certain plants, especially comfrey root.

Allantoin is generally to be found in plants and animals in the actively growing parts, and experiments on plants appear to show that it increases growth.

It is one of a class of drugs which have come into use as cell-proliferants. It is employed locally generally as a 0.4 per cent. solution to stimulate growth in sluggish wounds and sores.

MATERIA MEDICA

Caffeina. Dose, 1 to 5 grs. (6 to 30 ctgrms.).

Caffeinæ Citras. Dose, 2 to 10 grs. (12 to 60 ctgrms.).

Caffeinæ Citras Effervescens. —Containing citric acid, tartaric acid, and sodium bicarbonate. **Dose, 60 to 120 grs.** (4 to 8 grms.).

Theobrominæ et Sodii-salicylas (diuretin). Contains about 40 per cent. theobromine and 60 per cent. sodium salicylate. **Dose, 10 to 20 grs.** (6 to 12 dcgrms.).

Theophyllinæ Sodio Acetas. Dose, ½ to 2 grms.

Uvæ Ursi Folia.

PREPARATION

Infusum Uvæ Ursi. Dose, ½ to 1 oz.

Scoparium. *See under* " Drugs acting on Nerve-Cells."

Buchu. *See under* " Essential Oils."

URINARY ANTISEPTICS

Drugs are not employed to diminish the quantity of urine. Any mildly irritant drug which is excreted by the kidneys will induce slight irritation followed by vaso-dilatation and diuresis. But many of these irritant drugs in large dosage induce intense vaso-constriction, and may thus be the cause of anuria. Such drugs are cantharides and turpentine.

The reaction of the urine can be altered and the urine rendered alkaline by the carbonates, acetates, tartrates, or citrates of potassium, sodium, or lithium. The organic salts produce this effect, because they are oxidised in the body and excreted as carbonates.

Benzoic acid is sometimes employed to render the urine more acid. During its passage through the kidney it combines with glycocoll and is excreted as hippuric acid. It is not, however, very effective. Salicylic acid, which has also been used for the same purpose, is even less valuable. The best drug for this purpose is acid sodium phosphate, the natural acid of the urine, which renders it very much more acid.

Drugs are sometimes administered to prevent the deposition in the urinary passages of the solids of the urine, especially uric acid calculus, and in gout to aid in the excretion of uric acid. For this purpose alkalies are generally given, especially lithium carbonate, in which uric acid is most easily soluble.

Piperazine has the property of dissolving twelve times the amount of uric acid that lithium carbonate dissolves. Urotropine, which also dissolves large quantities of uric acid, has been employed to produce the same effect. Neither piperazine nor urotropine is of any value when used for this purpose. Piperazine, 0.2 per cent. in blood-serum—an amount never likely to be attained in the living body—has no effect in increasing the solubility of sodium biurate.

Efficient *genito-urinary antiseptics*, when taken in proper dosage by the mouth, should prevent the multiplication of organisms in the urine and on the surface of the mucous membrane of the urino-genital tract : it is not likely, however, that they will effect any permanent benefit in tuberculous conditions or in the later stages of gonorrhœa when the organisms are growing in the tissues beneath the mucous membrane.

The bacteria which infect the urinary tract may be divided into two groups according to whether or not they cause urea to be split up and so produce alkaline fermentation. The first group includes Bacillus coli, B. acidi lactici, B. typhosus, and others, and since they do not render the urine alkaline these organisms are found in acid urines. The second group comprises the pyogenic cocci and putrefactive organisms which when growing freely produce the foul alkaline urine often present in cystitis. Urinary antiseptics are all much more efficient against the first group than the second, since all act better in an acid urine.

Hexamina or hexamethylene tetramine is a condensation product of ammonia and formic aldehyde. When taken by the mouth it is rapidly excreted by the kidneys, and if the urine be acid a certain amount is split up by the acid, yielding free formaldehyde. Its antiseptic action is entirely due to this liberation of formaldehyde, and urotropine is therefore very efficient in a highly acid urine and quite useless in an alkaline one. It should therefore be given only when the urine is acid. If the urine be alkaline it may be first rendered acid by the dihydrogen sodium phosphate, and then the urotropine will be effective, but this drug has no antiseptic action of any significance except in the presence of acids. **Dose, 10 to 15 grs.**

Benzoic and Salicylic Acids have a distinct antiseptic action on the genito-urinary tract. They are less effective against B. coli than against cocci, and in acid urines their effect is very much less than that of urotropine.

Volatile Oils, particularly those of sandal-wood, copaiba, and cubebs, which are relatively non-irritant, are used as urinary antiseptics, especially in gonorrhœa. These drugs are much more efficient antiseptics against staphylococci than against B. coli and other bacillary infections, and moreover this action, though diminished, is not destroyed by an alkaline urine, so that these drugs may be legitimately employed when the urine cannot be made acid.

Sodium dihydrogen phosphate, NaH_2PO_4, the natural acid of the urine, is the most valuable drug to employ whenever it is desired to render the urine acid. Merely increasing acidity inhibits the rate of growth of all organisms in the urine and a high degree of acidity favours the action of most antiseptics in the urine.

MATERIA MEDICA

Sodii Phosphas Acidus. Dose, 30 to 60 grs. (2 to 4 grms.).

CHAPTER XI

GROUP OF CARDIAC TONICS

Digitalis. Strophanthus. Squill.

The contraction wave of the heart-beat in the frog originates in the great veins at the base of the heart and passes as a wave by the sinus venosus through the auricles to the ventricles. In mammals the contraction wave is believed to start in the right auricle from a point near the sinu-auricular node : the wave of contraction spreads from here in all directions by special conductile tissue to the auricles and by the auricular-ventricular bundle of His to the ventricles, where the conductile tissue spreads out and communicates with the ordinary cardiac muscle. This nodal and conductile tissue of the heart when acted upon by drugs produces a different effect on the heart-beat from an action on ordinary cardiac muscle. This tissue may be referred to conveniently as the excito-motor portion of the cardiac muscle. A drug which diminishes conduction through the bundle might fail to transmit certain of the auricular beats, and therefore the ventricular beat would be slower ; digitalis in certain conditions may possibly slow the beat in this way. Drugs which interfere with conduction may produce a condition of incoordinated muscular contraction, that is, the individual cardiac muscle fibres may be contracting at different times instead of synchronously, and a condition known as fibrillation is obtained.

Action of Drugs on the Heart.—The beat of the heart can be influenced by drugs in one of two ways : either the rate may be altered or the force and type of contraction may be changed.

In the first place, the heart-beat may be slowed by stimulating any part of the vagal mechanism. This can be brought about by directly exciting the medulla with such drugs as strychnine and aconitine, or, as we have seen already, by the sudden inhalation of a large dose of chloroform (Fig. 44, *A*). Also, the medulla may be excited reflexly by afferent impulses reaching it through the fifth and tenth nerves. Thus the inhalation of ammonia or acid vapour tends to slow the heart through irritation of the sensory endings, both in the nose (fifth nerve) and the sensory endings in the lungs (tenth nerve). Any considerable skin excitation, such as a very severe burn, produces the same reflex effect, whilst it is well known that psychical emotion may produce cardiac inhibition. Finally, the medulla is affected through the blood-pressure. Any cause

which tends to raise blood-pressure also tends to stimulate the medulla and so to slow the heart-beat. Thus adrenaline, which raises the pressure largely from vaso-constriction, and which has no direct action on the medulla, also slows the heart-beat, especially when the pressure is at its highest. In these cases no cardiac slowing is obtained if the vagi are either severed, or paralysed by the use of atropine. Secondly, the vagal mechanism can be excited through the intra-cardiac ganglia by such drugs as nicotine, coniine, and lobeline (Fig. 44, *B*). The stimulation is only transient, and to observe the effect the drug should be injected into the circulation. Thirdly, the vagus can be excited through its endings in cardiac muscle (Fig. 44, *C*). Several drugs have this action, including the members of the digitalis group, physostigmine and pilocarpine. Any cause which tends to depress the excito-motor apparatus would tend also to slow the heart, but we know of no drugs which in therapeutic doses produce this effect. Finally, drugs which produce mild excitation of the ordinary cardiac muscle also slightly slow the heart-beat. Thus digitalis slows the heart a little, even when the vagal endings are paralysed by atropine.

Acceleration of the heart can be brought about by any of the reverse processes to those just described, and, in the first place, by stimulating some portion of the accelerator mechanism. As this mechanism is augmentor as well as accelerator, it follows that drugs which act in this way generally increase the force as well as the rate of the beat. We know little concerning the action of drugs on the more central portions of this mechanism, but on the nerve-endings in the heart several drugs act (Fig. 44, *D*). Adrenaline is the best example of these. This drug when introduced into the circulation both accelerates and increases the force of the heart-beat. The effect is not obtained if the sympathetic nerve-endings are paralysed. Pilocarpine administered by the mouth in medicinal doses also slightly quickens the pulse, and it is probable that this is brought about in the same way; and the increased pulse-rate observed after taking cocaine affords a third example. A second method of accelerating the heart-beat is to depress the inhibitory mechanism. This may be done by drugs acting either on the medulla, the nerve-cells in the heart, or the nerve-endings. Anæsthetics and narcotics depress the medulla and so tend to quicken the heart: chloral and chloroform, during the anæsthetic stages, afford examples of this. The heart may be accelerated reflexly through the medulla by any mild stimulus applied to the skin. Thus an ordinary blister or mustard-plaster produces a distinct increase in the rate. Again, it should be remembered that any cause which brings about a lowering of blood-pressure tends to quicken the heart by diminishing the tonus of the medulla; and some of the quickening seen after taking a nitrite is due to this cause.

Secondly, the nerve-cells on the course of the vagus are depressed and, in large doses, paralysed by such drugs as nicotine, coniine, or lobeline; and one of the features of nicotine-poisoning is a rapid pulse. Thirdly, the vagal nerve-endings are depressed or paralysed by the alkaloids atropine, hyoscyamine, and hyoscine. But whether the depression is central, at the nerve-cells, or the nerve-endings, the heart-beats quicken, and the increased rate depends on the extent of the medullary tonus. There is still another method

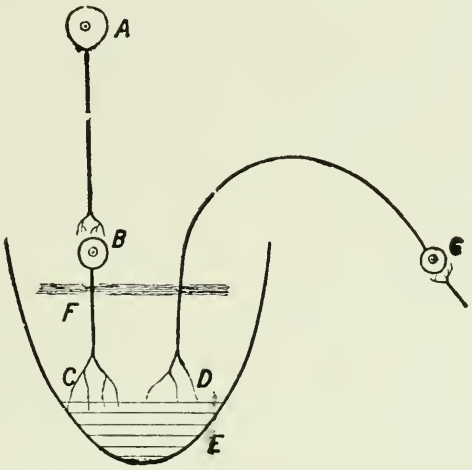


FIG. 44.—DIAGRAM SHOWING THE INNERVATION OF THE HEART.*

A = Vagal centre in the medulla; *B* = Intra-cardiac ganglion on vagus; *C* = Vagal endings; *D* = Sympathetic endings; *E* = Cardiac muscle; *F* = Excito-motor area (nodal tissue and bundle of His); *G* = Ganglion-cell on the course of the sympathetic nerve.

Table of Drug Actions

A. Strychnine +, aconitine +, picrotoxin +, HCN + −, cornutine +, chloral and hypnotics −
B. Nicotine + −, coniine + −, gelsemine −.
C. Pilocarpine +, physostigmine +, digitalis +, atropine −.
D. Adrenalin +, cocaine +, pilocarpine +, tyramine +.
E. Barium +, calcium +, veratrine +, digitalis +, lead +, chloroform −, chloral −.
F. Caffeine +, aconitine +. Digitalis in poisonous doses.
G. Same as *B*.

(+ represents stimulation and − depression.)

by which the drugs can accelerate the heart, namely, by acting on the cardiac muscle. It is well known that there is a portion of the heart, corresponding to the sinus venosus in the frog, excitation of which quickens the beat; this is spoken of as the excito-motor portion of the muscle (Fig. 44, *F*). We have already seen that many drugs which in small doses attack ordinary cardiac muscle produce some slowing; now if these drugs are given in larger doses the action spreads to the excito-motor portion of the heart, and acceleration follows. The beat becomes quicker and quicker, and ultimately the heart enters into fibrillary twitchings (delirium cordis). Every drug which excites cardiac muscle produces this effect if

* Some sympathetic fibres have their cell stations in the heart; for clearness these are not shown.

given in poisonous doses. Some drugs which act on the heart-muscle exert their initial effect, not on the ordinary muscle (*E*), but on this excito-motor area (*F*). Caffeine and the purine derivatives are perhaps the best known of these; the smallest doses of these drugs tend to quicken the isolated heart. Aconitine is another drug which in big doses acts on the excito-motor area before the ordinary cardiac muscle, and kills the heart by sending it into fibrillary twitchings.

We have to consider now how alterations in the force of contraction of the heart can be brought about. It has been already observed that drugs which excite the accelerator mechanism increase the force of contraction. The same result may be attained by drugs such as barium and veratrine, which directly excite cardiac muscle. They produce a more prolonged, a more vigorous, and a more perfect systole, and an imperfect relaxation; and in the frog—the heart of which does not enter into fibrillary twitchings—the extent of diastole becomes less and less, until ultimately there is standstill in systole.

It now remains to state the meaning of the term "cardiac stimulant." In order to make this plain, let us examine a common case of cardiac disease in which the mitral valve is incompetent. When the left ventricle contracts, some of the blood regurgitates through the mitral valve into the left auricle, and so produces back-pressure on the right side of the heart and therefore general venous congestion. Sufficient arterial blood does not pass through the coronary vessels and the heart is not properly nourished; so the muscle degenerates and the heart dilates. Such a heart will be found to be beating inefficiently but very rapidly. The ventricle is so feeble that the heart never empties itself, and as compensation for this the rate is increased. If, now, we administer a cardiac stimulant (a member of the digitalis group of drugs) the force of contraction and the tonus of the muscle are increased so that the heart empties itself more completely. Digitalis also stimulates the vagus mechanism and so the diastolic phase is longer; hence, each systole is more vigorous and prolonged, so that relatively more blood passes up the aorta, and the heart is slower. In a word, the heart is not made to do more work, but it is made to do more useful work. A general rule in the treatment of disease is to give the affected organ as much "rest" as possible, and here, as elsewhere, the rule holds; digitalis in small doses rests the heart by increasing diastole.

The force of the beat may be changed by altering the peripheral resistance in the arterioles; this will be considered later.

Cardiac depression, *i.e.* diminution of the force of contraction, can be brought about by any drug which depresses the cardiac muscle; chloral, chloroform, and potassium salts will serve as examples.

DIGITALIS

Digitalis or foxglove leaves are obtained from the plant *Digitalis purpurea*, and should be gathered in the autumn. The chemistry of digitalis is most unsatisfactory. A number of glucosides can be extracted, of which digitoxin possesses the characteristic action of the drug on the heart, and is the most toxic. Another glucoside is digitonin, which is a member of the saponin group, and possesses all the properties of these bodies. Although it is not absorbed from the alimentary canal it is of considerable importance, as it aids in the solution of some of the other glucosides. Digitalin has a similar action to digitoxin, but is weaker. Digitalëin is a name given to yet another glucoside with a somewhat doubtful composition; it is soluble in water, and may possibly be a combination of the other glucosides with digitonin.

In the tincture these glucosides occur combined with tannic acid (digitannoids); and in this form their solubility and absorption are different from the artificially isolated glucosides.

Too much stress should not be laid on these different glucosides; they are very unstable and can only with much difficulty be prepared absolutely pure.

Out of all this confusion we have one valuable chemical fact: we can always prepare from good digitalis leaves a certain quantity of active digitoxin, but it is impossible to estimate the amount and so standardise the drug chemically, as the different methods give very different results, and the glucosides are unstable. Further, the samples of digitoxin at present on the market vary in activity even more than the galenical preparations. The physiological method is the only one at present available for standardising this drug.

Two fluid preparations of digitalis are used in medicine: an infusion and a tincture. Now digitoxin and digitalin are insoluble in water but soluble in alcohol, whilst the less active glucosides are said to be soluble in water. Nevertheless, the infusion contains some digitoxin and digitalin in colloidal solution, this result being brought about by means of the digitonin. The glucosides of digitalis readily undergo decomposition and form resin-like bodies; that resulting from digitoxin is termed toxiresin, and that from the others, digitaliresin. The changes occur especially in old specimens and are probably caused by bacterial action. These resins produce convulsions by acting on the medulla, and act precisely like picrotoxin. Old preparations of the infusion are, therefore, not only useless but absolutely harmful, since the resins which are formed are more toxic than digitalis.

We will take digitalis as a typical member of this series and describe its action fully, and subsequently note any differences between it and that of other members of the group.

Action

Externally digitalis is intensely irritant, and when applied to any of the mucous membranes gives rise to inflammation and pain. Subsequently, like most protoplasmic poisons, it paralyses the sensory nerves. Its intensely irritant nature can be well seen by injecting some of the British Pharmacopœial tincture subcutaneously, when inflammation ensues, and may even give rise to abscesses ; or if 5 c.c. of the tincture is placed in the stomach of an anæsthetised or decerebrate animal, and left there about two hours, an examination of the stomach will reveal acute inflammation, and very probably ulceration also ; so that the irritant action of the drug is of a peculiarly virulent type. This effect is due to the digitoxin ; the digitalin is much less irritant.

Digitalis is absorbed slowly from the small intestine : therapeutic effects, especially diuresis, are rarely observed until forty-eight hours after commencing a course of treatment.

Under normal conditions digitalis is resistant to digestive ferments, but in cardiac disease associated with venous congestion absorption is delayed and probably some destruction of the glucosides occurs, but in any case the action is much reduced.

It exerts its principal action on the circulatory system. In small doses it always slows the rate of the beat. This is partly due to excitation of the medulla, because if the vagi are previously severed the slowing is not so great. Digitalis will slow the beat of the isolated heart, and this is due mainly to an effect on the vagal endings, because if these are paralysed by atropine, digitalis no longer produces much slowing. But even in the atropinised heart digitalis still induces a slower beat, which is the result of the action of the drug on cardiac muscle.

Digitalis is used in medicine in cases of failing circulation: in these cases the output from the heart is generally deficient, the veins are engorged, and the venous pressure high. Digitalis fills the arteries and empties the veins; but in the normal circulation the arteries are already efficiently filled and digitalis therefore produces relatively little effect. Nevertheless, it will be well to examine the action of digitalis on normal tissue and then we can use the knowledge to explain the action in disease.

If a record is taken of the movements of the heart of a decerebrate frog, and if when the beat is regular a subcutaneous injection of digitoxin is given, a well-defined series of events occur. The heart-beat becomes slower due to longer diastole; this gives more time for the heart to fill completely and gives rest. The ventricular contraction becomes more powerful, and the heart empties itself during systole more completely than in the normal state. That is, the individual muscle fibres shorten more, but the force of contraction as measured by the height to which the heart can raise a column of liquid is not increased (Fig. 45).

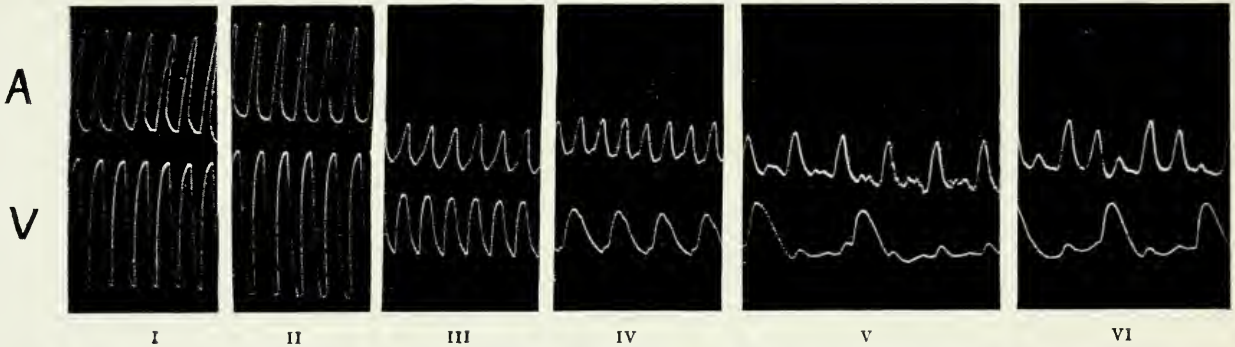


FIG. 45.—RECORD OF AURICLE AND VENTRICLE OF FROG'S HEART.

Shows the effect of an injection of digitoxin into the dorsal lymph sac. I, normal. II, the after injection. Note the longer diastole and increased systole. III, half an hour later. Note that in diastole the ventricle is semi-contracted. IV, fifteen minutes later. Shows two auricle beats to each ventricular. V and VI show complete inco-ordination between auricle and ventricle. Time, 1 in. = 10 secs.

To face p. 173.

If the dose of digitoxin has been large a further effect appears: the diastole gradually becomes less complete until a stage is reached when during complete diastole the heart is in a semi-contracted condition (III.). Later conduction disturbances supervene, two or more auricular beats occurring for each ventricular (IV.); and still later the ventricular muscle beats irregularly and co-ordination between the different parts of the heart is lost, so that parts of the ventricle may be in contraction whilst other parts are in relative relaxation. Ultimately the ventricle stops in systole whilst the auricles continue to beat.

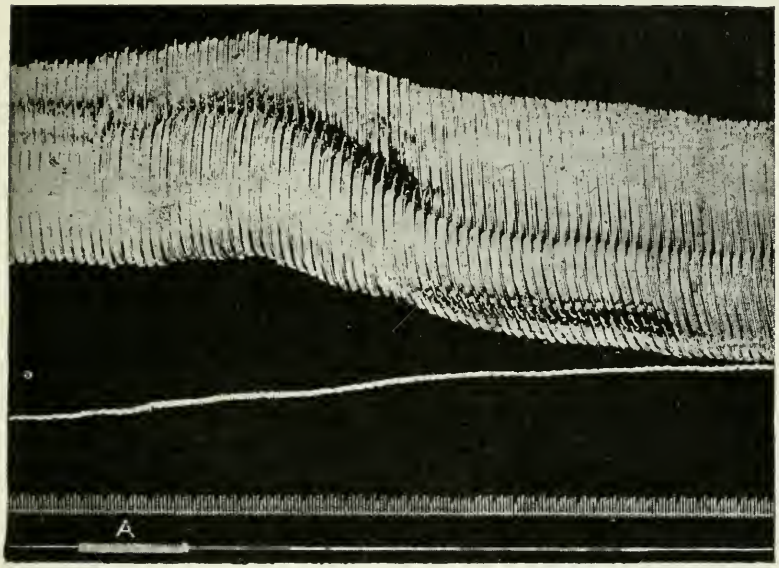


FIG. 46.—CAT (DECEREBRATE). CARDIOMETER AND B.P.

At A 5 m. of tincture of digitalis were given by a vein. Note the more complete systole (downstroke) and the increased output of blood per beat (total height of curve). B.P. rises mainly because of the increased cardiac output. Time = secs.

In the isolated mammalian heart the same effects can be elicited, but the cardiac slowing is not so decided as it should be because there is no vagal centre (Fig. 47). Nevertheless some slowing is seen together with a more efficient beat, the heart both filling and emptying more completely. This stage, as in the frog, is followed by conduction disturbances and death in systole.

If we pass now and examine the mammalian heart in the intact animal we find that the same facts hold good; further, as the dose is increased to within poisonous limits, cardiac effects are produced which are due either to an excessive inhibitory or to an excessive muscular action. We can, therefore, divide the action of digitalis on the heart of a man into three stages:—

Stage 1 is the therapeutical, in which the heart is moderately slowed, and in which it fills and empties more completely. This effect can be shown experimentally on animals in a variety of ways; perhaps the best is by means of the cardiometer. This is a glass bulb, which is fitted round the heart between it and the pericardium and made air-tight by vaseline. When this cardiometer is connected to a recorder the volume changes of the heart are determined. As the heart fills with blood the recording lever rises, and as the heart empties the lever falls. Fig. 46 shows the effect of digitalis on a cat's heart, the movements of which have been recorded in this way. The output of blood, as measured by the vertical lines, is increased considerably during each beat, and the shortening in systole is greater.

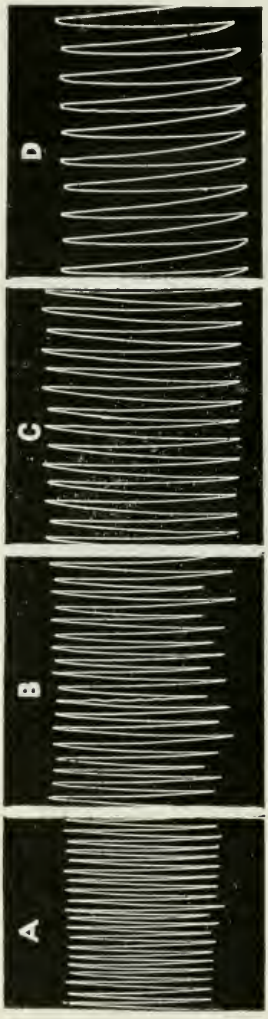


FIG. 47.—MOVEMENTS OF THE ISOLATED RABBIT'S HEART PERFUSED WITH RINGER'S SOLUTION.
Upstroke = systole. A shows the normal beat. B shows the condition after perfusion for ten minutes with 1 in 2500 tinct. digitalis; systole is greater and more prolonged, and diastole is increased. C was taken fifteen minutes later and all the effects are more decided. D was taken thirty minutes after perfusion: in this case the slowing is very pronounced. Later the heart stopped in systole.

The actual contraction of the cardiac muscle can be determined in the intact animal by attaching a thread to the apex, say, of the left ventricle, and connecting this over a pulley to a weighted lever, so that each contraction of the ventricle induces a movement upwards of the lever. Digitalis in therapeutic doses increases both the upstroke and downstroke of such a system, but especially the upstroke. Perhaps the effect on the ventricular muscle is best determined by perfusing the isolated heart through the coronary arteries with Ringer's solution, and recording the movements of the ventricle by a thread attached directly to the heart and to a lever. Fig. 47 represents such a tracing and demonstrates the typical digitalis action. In experiments of this type it can be readily shown that the mammalian heart, like the frog's heart, dies in systole.

These experiments show that in the intact mammal digitalis

increases the degree of contraction of cardiac muscle, including papillary muscle: as a result of this, systole is more perfect, the ventricles empty more completely, and the output of blood from the heart is increased, whilst the slowing, in moderation, gives more time for complete filling. To sum up, the arterial system is filled and the venous pressure falls as the blood finds an easy outlet into the empty heart. This change in the distribution of blood is not well shown in the normal animal in which the circulation is already perfect. Evidence for the human ventricle of those systolic and diastolic effects of digitalis which are fundamental actions on the isolated heart must be the clinical observation of the redistribution of the blood from the venous to the arterial side of the circulation, with shrinking of the swollen liver, absorption of œdema with diuresis, and relief of pulmonary stasis and its attendant dyspnœa, all of which are common features in cases of cardiac failure.

Digitalis exerts its most pronounced effects on the heart, in mitral disease with dilatation and the resulting back-pressure effects such as congestion of the lungs, liver, kidneys, and dropsy. The heart in such a condition is almost always very rapid, and digitalis produces its beneficial action as follows:—In the first place, it prolongs diastole and rests the heart: secondly, it acts on the cardiac muscle and produces a more efficient systole, and so forces more blood through the coronaries; as a result of the latter effect it improves the nutrition of the heart. It is probably for this reason that an irregular heart becomes regular.

Though we have not drawn special attention to the auricle its movements are modified in the same way as those of the ventricle, relaxation is hardly altered, but contraction is more complete.

Digitalis often benefits most those patients in whom the auricles are fibrillating. The term fibrillation is applied to a condition of the muscle of the heart in which the individual fibres, instead of contracting in an orderly manner during systole, contract independently of one another. Auricular fibrillation is a well-recognised clinical condition and does not cause death. Ventricular fibrillation is followed immediately by a fall of blood-pressure to zero and death. Chloroform, digitalis, caffeine, and potash salts may all cause this loss of co-ordination and death. The slowing of the heart by digitalis in cases of auricular fibrillation is not due to stimulation of the inhibitory mechanism, for the effect is still obtained even when the patient is under atropine. It is probable that digitalis by acting on the muscle improves the nutrition of the heart, it may be by increasing the coronary circulation; as the nutrition becomes more normal, so will the rate of the beat become normal. One other explanation has been suggested to account for this action: digitalis is said to act by producing a partial heart block; that is, it depresses the conductile tissue in the bundle of His. In cases of auricular fibrillation a large number of feeble

auricular beats are imperfectly transmitted to the ventricles, and it is suggested that digitalis by depressing conductile tissue allows only a few of these impulses to get through (Fig. 48).

Fibrillation is never transferred as such from auricle to ventricle, but the ventricular muscle beats in a co-ordinated fashion though the beat is irregular. The responses are the result of impulses traversing the bundle of His and escaping haphazard from the quivering auricle.

Stage 2.—Two stages of poisoning by digitalis are known. In the stage in which an excess of inhibition overshadows for the time being the muscular effect the heart-beat is irregular and slow, but, provided the effect is not very great, the output at each systole is still greater than normal, since the prolonged diastole gives ample time for the ventricles to fill. But sometimes the inhibition is so powerful that the muscular action of the drug is overshadowed and the systole is actually weaker than normal. Not uncommonly extra systoles occur: these are feeble contractions which open the valves but give rise to no pulse waves, so that the number of beats counted at the wrist and with the stethoscope is different. This stage in digitalis poisoning can be abolished by an injection of atropine, which depresses the inhibitory apparatus by acting on the vagal nerve-endings.

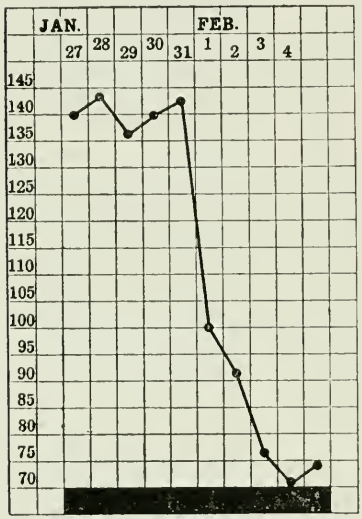


FIG. 48.—CHART.

Showing a typical reaction of digitalis in a case of auricular fibrillation with severe heart failure and rapid pulse-rate. The administration of the digitalis began on January 27, in doses of 15 m. four times daily. (Mackenzie.) The dark line shows the period during which digitalis was administered.

Stage 3.—Very large doses of digitalis produce fibrillary twitchings of cardiac muscle. First, the heart increases in rate, not on account of any vagal action, for acceleration is still induced even when these nerves are atropinised. The condition is probably due to an action on that part of the cardiac muscle termed the excito-motor (nodal) area. As the acceleration increases the heart beats in an extremely irregular fashion, and the output per beat varies considerably on account of the absence of sequence between auricles and ventricles (Fig. 50, D). Nevertheless, during the early part of this stage the output from the heart per minute is increased on account of the greater rate. But as the acceleration and arrhythmia continue relaxation becomes less and less perfect, and the heart ultimately enters into fibrillary twitchings and dies in systole.

Whenever an organ is made to perform an excess of work over the normal and for a prolonged period, it hypertrophies. Thus, if one kidney is removed the other hypertrophies to take its place. So, if an animal is given digitalis every day for two or three months, and is then killed, its heart as compared with controls from animals in the same litter shows decided hypertrophy, and is

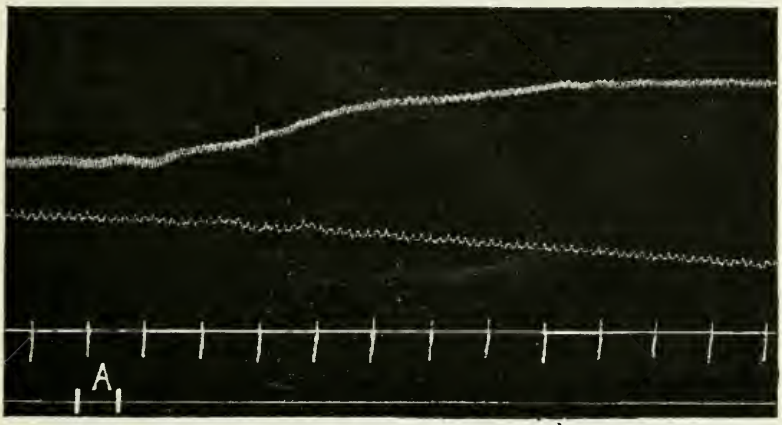


Fig. 49.—Cat. The Upper Tracing represents B.P. and the Lower the Volume of a Small Loop of Intestine.

At A 7 m. tinct. digitalis were given by a vein. The intestinal volume slowly diminishes as the result of vaso-constriction. The blood-pressure rises partly from the vaso-constriction and partly from the increased cardiac output. Time = 12 secs.

greater in weight. This factor should not be neglected in therapeutics.

The vessels are constricted by digitalis, and the action is both peripheral and central. Vaso-constriction can be shown in an intact animal by enclosing some abdominal viscus in an oncometer and then injecting the drug; the volume of the viscus shrinks in spite of the rise in blood-pressure, and such immediate diminution in volume can only be vascular (Fig. 49). The same result may be obtained in man by placing one arm (preferably that of someone with a low blood-pressure) in a suitable oncometer and injecting digitalis as before; in this case the vaso-constriction is best recognised by the diminished volume-pulse. The constriction is partly central in origin, because it is decidedly less after section of the splanchnic nerves; but a considerable amount is due to the direct action of the drug on the muscle of the arterioles. If defibrinated blood is perfused through the vessels of the isolated kidney, intestine, or limb of a cat or rabbit, and the outflow measured every ten or twenty seconds, then the addition of digitalis to the perfusing fluid at once diminishes the outflow as a result of the constriction.

The coronary renal and pulmonary arteries are said to be less affected than the others.

It now remains to observe how these vascular changes affect blood-pressure. In the therapeutic stage blood-pressure slightly rises, both on account of the vaso-constriction and the increased output from the heart (Fig. 50, B). More blood is forced out from the heart into the vessels and meets perhaps with more resistance than usual, so that the arteries fill with blood and the veins empty quickly. The volume of any viscus, such as the kidney, will thus assume the mean between these two factors (Fig. 52). It tends to dilate, since the heart is pumping out more blood, and it tends to contract, on account of the vaso-constriction. The resultant is a moderate constriction of vessels with an increased velocity of blood-flow.

If there is an excess of inhibition, as in *Stage* 2, the output from the heart may be so much diminished as to produce a fall of blood-pressure. During the acceleration in the final stage (Fig. 50, D) the blood-pressure again rises, but as the arrhythmia increases it slowly falls again, until quite suddenly it drops to zero, and the heart is found to be in fibrillary twitchings. The relative action of digitalis on different vessels has been considered already; the coronary arteries become constricted in the later stages of poisoning, and may cause death by limiting the blood-supply to the heart.

It must be remembered that any increase in peripheral resistance resulting in an augmented blood-pressure involves more work for the heart, and therefore any considerable rise in blood-pressure from this cause in cases of cardiac disease is undesirable. From clinical experience we know that digitalis has very little effect on the blood-pressure of patients suffering from cardiac disease.

Digitalis has an action also on other forms of plain muscle. It increases tonus and stimulates the activity of the ordinary automatic movements. When given by the mouth or injected it induces increased movements of the stomach and vomiting. This is a peripheral effect, probably on the vagal nerve-endings. Similar changes are induced on the rest of the gut ; peristalsis is increased and diarrhœa follows. All these effects are peripheral, since the changes can still be observed in the isolated and artificially perfused gut. The uterine movements are similarly influenced, and when the organ is pregnant abortion may ensue. The tonus of the bronchioles, spleen, and other plain muscle in the body is also increased.

It must be remembered that these effects are of relatively small importance when medicinal doses of digitalis are being employed, and when they are to be seen, they indicate that the amount of drug which is being absorbed is excessive and the administration should cease for a time.

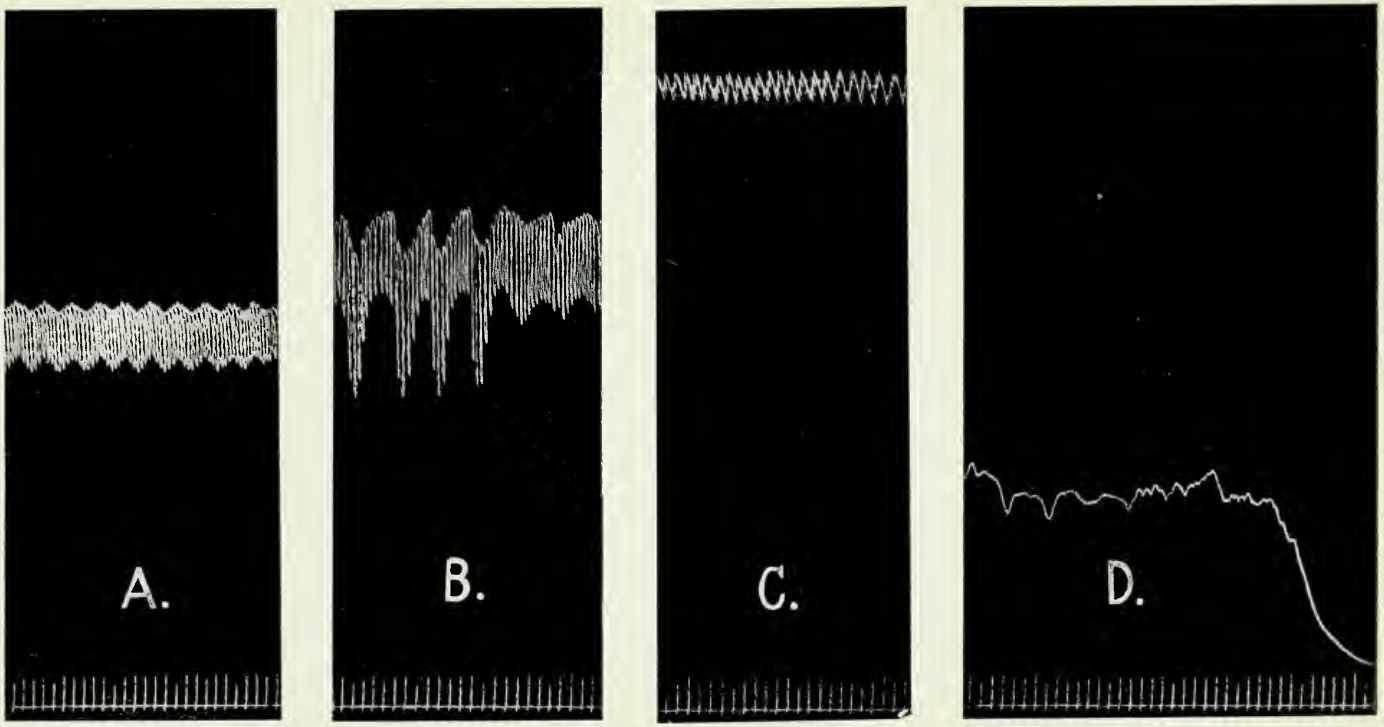


FIG. 50.—CAT. BLOOD-PRESSURE TRACINGS.

Urethane employed as an anæsthetic. A normal. A large dose of tinct. digitalis was then given subcutaneously (60 m.). B shows the effect five minutes later; this represents the typical therapeutic stage—the heart-beat is slower, but the blood-pressure is higher. C represents a later stage in which the heart is very rapid but still regular, and hence the great rise in blood-pressure. D shows the last stage, in which the heart is extremely rapid but at the same time irregular, so that the output is diminished and the blood-pressure falls. Death is shown occurring suddenly from delirium cordis. Time = secs.

To face p. 181.

The central nervous system is stimulated, the effect being especially on the medulla. Respiration is deeper and quicker, the heart is slowed, and the vaso-motor centre excited. The vomiting which follows the administration of large doses of digitalis is mainly peripheral in origin, although, no doubt, the medulla is more excitable to reflexes. After very large doses of digitalis convulsions are sometimes obtained, which are comparable in every way with those produced by picrotoxin. We have seen already that the blood-vessels of the brain are passive, and their state of distension is determined entirely by the blood-pressure.

In the specific fevers and in conditions where there is reason to believe the central nervous system is affected, digitalis sometimes loses its power of slowing the heart whilst it still produces its normal effect on the cardiac muscle. In such cases if the drug is pushed poisoning is apt to ensue.

Digitalis is sometimes employed as a diuretic in cardiac disease, especially in those cases of mitral disease which are accompanied by dropsy and venous congestion, and in which very little urine, perhaps only a few ounces a day, is being passed. In these cases the diuresis from digitalis is very decided, and must be regarded as entirely due to the improved circulation. The venous congestion gradually passes off and the kidney again receives a good supply of arterial blood, to which it responds by a free secretion of urine. If digitalis is given to a healthy man it does not behave as a diuretic, or at most only increases the urine by a few ounces. If a dose is given to an animal in which the kidney volume and the excretion of urine are measured simultaneously, it is found that the flow of urine may be slightly increased at a time when the renal vessels are constricted. It is probable, however, that in this case the increased blood-pressure ensures that, in spite of vaso-constriction, more blood passes through the kidney than normally. If very large doses of digitalis are administered the vaso-constriction may be so great as to decrease or completely inhibit excretion. The greater flow of urine is mainly an increase in the water ; the salts and urea are not augmented proportionately.

Digitalis is very slowly excreted, probably partly from the intestines and partly in the urine; its excretion may be even slower than its absorption, so that its continued use is liable to lead to cumulative effects. Sometimes during a course of the drug symptoms of poisoning suddenly develop. The pulse becomes very irregular and slow, vomiting and diarrhœa supervene, and the patient feels very weak and faint. Any accidental cause, therefore, which tends to diminish the excretion or promote absorption might lead to cumulation and symptoms of poisoning. The symptoms are rarely serious if observed in time. The glucosides are fixed by the heart, and the degree of digitalis action depends on the amount so stored up. If a little digitoxin is perfused through the coronary vessels of an isolated rabbit's heart for ten seconds only, though

little effect is produced at first, poisoning gradually ensues and the heart dies in systole two or three hours later. The glucoside does not pass out with the perfusing fluid but is retained by the heart for a considerable time, so that by the continuous administration of digitalis cumulation may occur.

Cumulation may be studied by injecting into animals a subminimal lethal dose of the drug to be tested and at some later period determining what additional dose must be injected to make up the lethal dose. Thus if a time is chosen for the second dose when all the drug has been excreted from the preliminary dose, then a full M.L.D. (minimal lethal dose) will be required to kill the heart; but if only half has been excreted then the difference between the ordinary M.L.D. and the fraction remaining in the body only will be required.

By this method it has been found that twenty-four hours after an injection of strophanthin three-fourths has been excreted, and five days after injection all has gone from the body. Digitoxin, on the contrary, is retained in the body for a much longer period: nearly 50 per cent. of the amount injected is still present after five days, and even after twenty days some still remains. The other digitalis glucosides are excreted more quickly, excretion being generally complete in about a week. In the case of the Galenical preparations it is found that about 25 per cent. is still present in the animal after ten days.

Digitalis preparations are directly irritant to the stomach, are cumulative, and cannot be given hypodermically without pain and inflammation, hence many substitutes have been advocated. Digitoxin (Schmiedeberg) and Digitalin (Nativelle), both true digitoxin, are too irritant for injection, are insoluble in water, and have no advantages over galenical preparations. Digalen is probably a mixture of digitoxin and digitalin ; it is soluble in water, but has no other advantages. All the soluble commercial " digitalins " are mixtures generally of digitalin and digitonin. Digipuratum is an extract from which inert matter and saponin have been removed. It is perhaps the best of the substitutes : it is soluble in dilute alkalies, is less irritant to the stomach, through which it passes unchanged, than digitalis, and can be injected intravenously.

MATERIA MEDICA

Digitalis Folia. **Dose, ½ to 2 grs.** (3 to 12 ctgrms.).

PREPARATIONS

1. **Infusum Digitalis.** **Dose, 2 to 4 drs.** (7 to 15 mils).
2. **Tinctura Digitalis.** **Dose, 5 to 15 m.** (3 to 10 decimils).

STROPHANTHUS

The seeds of *Strophanthus kombé*, the Kombé arrow poison, are official. The active principle is the crystalline glucoside strophanthin, $C_{40}H_{66}O_{19}$, which may be present up to 3 per cent. Other constituents of the seeds are choline, oil, and resin. In some species of strophanthus, "pseudo-strophanthin," $C_{40}H_{60}O_{16}$, is present, and is stated to be more active than strophanthin. This drug contains only one glucoside which is moderately easy to prepare, but it is not possible to use a standard preparation as the activity of the strophanthin varies greatly. Strophanthin differs from digitoxin in that it is easily destroyed by digestive ferments, so that given by the mouth it may lose much of its action.

FIG. 51.—TRACING OF A FROG'S HEART WHILST PERFUSED WITH RINGER'S SOLUTION.
Upstroke represents systole. The first eight beats of the tracing are normal and then the perfusion fluid was changed so as to contain 1 in 100 tinct. strophanthi. The heart stops in systole.

The action of strophanthus on the heart is very similar to that of digitalis, but it has a much smaller effect on the peripheral nerve-endings and on the central nervous system.

It was at one time used as a local anæsthetic for the eye, but it is slightly irritant, and although this is insignificant compared with the irritation of digitalis, yet this use of the drug has been superseded by the introduction of cocaine. On the stomach, intestines, and uterus it produces much less effect than digitalis, and its stimulant action on the medulla is also relatively small when compared with the former drug. It is absorbed more rapidly and is less likely to produce inflammation of the stomach than digitalis; it is also excreted sufficiently rapidly to prevent cumulative effects. When it is desired to produce a rapid digitalis effect in patients, when time is of vital importance, $\frac{1}{250}$ gr.

of the glucoside strophanthin may be injected intravenously, when the effect should be noticeable in from twenty minutes to one hour. When the desired action is obtained the patient may be put on a course of digitalis by the mouth.

Perhaps the most important difference between the two drugs is the action on the vessels. Digitalis produces marked peripheral vaso-constriction, whilst strophanthus is almost without such peripheral action. Strophanthus acts on the heart in almost the same way as digitalis, and produces the same effects. Fig. 51 shows the effect of strophanthin on the heart of the frog, which it stops in systole.

As this glucoside produces so little effect on the peripheral vessels, and as it raises the blood-pressure, it should send more blood through the kidney, and act as a more efficient diuretic than digitalis, and this we find to be the case. Strophanthin is diuretic even in the normal animal, because it raises the blood-pressure without constricting to any decided degree the renal vessels. Strophanthus is a much more powerful muscle-poison than digitalis: when applied directly to a voluntary muscle of the frog it rapidly produces rigor.

MATERIA MEDICA

Strophanthi Semina.

PREPARATIONS

1. **Extractum Strophanthi. Dose, $\frac{1}{4}$ to 1 gr.** (10 to 60 mgrms.).
2. **Tinctura Strophanthi. Dose, 2 to 5 m.** (12 to 30 centimils).

SQUILL

Squill is the bulb of *Urginea scilla*. It contains three bitter glucosides—scillitoxin, scillipicrin, and scillin. Scillin is crystalline, and has not a digitalis-like action, but the other two, which are amorphous glucosides, produce the characteristic cardiac effect.

Squill acts more powerfully on the heart than digitalis, but not so powerfully as strophanthus. This can be shown by perfusing the isolated mammalian heart with a solution of 1 in 2500 of the three respective tinctures in Ringer's solution. The heart which has had squill dies in about eighty-four minutes, the one with strophanthus generally in fifty or sixty minutes, and the one with digitalis does not die till after two hours, but in each case the death occurs in systole. Further, squill injected into the circulation of an intact animal induces a very much larger rise in pressure than can be obtained with digitalis (Fig. 52). In any case where it is desired to raise blood-pressure squill should be injected in preference to digitalis. In cardiac disease, however, it is not desirable to raise blood-pressure, since this must entail more work for the heart at a time when it is generally advantageous to put as little strain on the heart as possible.

The type of action on the heart is the same as that of digitalis.

On the blood-vessels the action of squill is again more marked than that of digitalis; nevertheless, its effects do not last so long, and this is apparently to some extent due to the more rapid absorption of the drug: cumulative effects are very rare.

Like digitalis, squill has an irritant action on all forms of plain muscle, but this is not so marked as that of the former drug. In big doses it produces nausea and vomiting like digitalis, and was at one time used in therapeutics as an emetic. In smaller doses it mildly irritates the stomach, and produces reflex secretion from the bronchioles: in practice it is used to produce this expectorant action. Administered by the mouth squill is absorbed much less

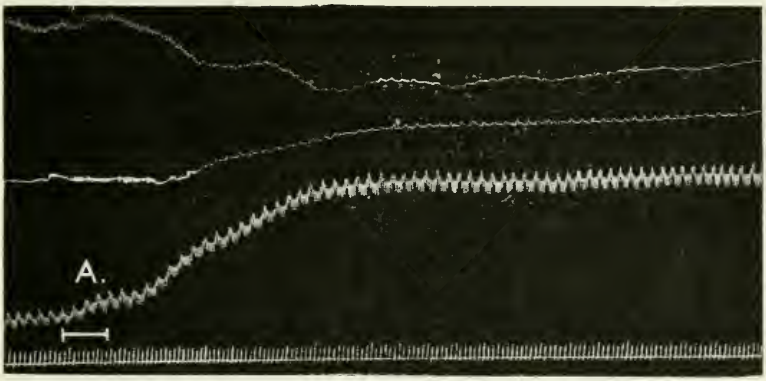


FIG. 52.—CAT. INTESTINAL VOLUME, LIMB-VOLUME, AND B.P.

At A 5 m. tinct. scillæ were injected into a vein. The intestinal vessels constrict and the blood-pressure rises, the total effect being greater than could be obtained by an equal amount of tinct. digitalis. The augmented blood pressure fills the limb-vessels, and in spite of their own tendency to constrict, the limb-volume increases. If the blood-pressure only rises slightly the constriction in the limb-vessels is evident. Time = secs. The lungs, brain, and liver always behave passively to the blood-pressure and so are congested by this group of drugs.

completely and more slowly than either digitalis or strophanthus, and perhaps it is for this reason that its cardiac action has not been recognised. In its other actions squill resembles digitalis.

There are a number of other plants which contain glucosides belonging to this group. These include convallaria (roots of lily of the valley), apocynum (Canadian hemp), and various species of cactus.

MATERIA MEDICA

Scilla. Dose, 1 to 3 grs.

PREPARATIONS

1. **Acetum Scillæ. Dose, 5 to 15 m.** (3 to 10 decimils)
2. **Oxymel Scillæ.**—Containing honey. **Dose, ½ to 1 dr.** (2 to 4 mils).
3. **Syrupus Scillæ.**—Acetum Scillæ, and sugar. **Dose, ½ to 1 dr.** (2 to 4 mils).

4. Pilula Ipecacuanhæ cum Scilla.—Squill, compound ipecacuanha powder. *See* Opium. **Dose, 4 to 8 grs.** (25 to 50 ctgrms.).
5. Pilula Scillæ Composita. **Dose, 4 to 8 grs.** (25 to 50 ctgrms.).
6. Tinctura Scillæ.—Squill, 1 ; alcohol (60 per cent.), 5. **Dose, 5 to 15 m.** (3 to 10 decimils).

BLOOD-PRESSURE

The blood-pressure may be regarded as dependent on three factors : (1) the amount of fluid contained in the vessels ; (2) the output from the heart per minute ; and (3) the resistance in the peripheral circulation. It is possible to modify blood-pressure by altering any of these three factors. Bleeding in any form (venesection, leeching, cupping, &c.), though a temporary measure, is the most powerful of all for reducing blood-pressure. The perfusion of salt solution into a vein is likewise the most rapid of all measures for raising the blood-pressure. But, in an emergency, when the apparatus for perfusion is not to hand, the same effect may be attained by the injection of a large quantity of saline solution subcutaneously or into the rectum.

Many drugs increase the output from the heart, especially the group of cardiac tonics which we are now considering ; but these drugs also constrict the peripheral vessels, so the rise in blood-pressure which they produce is a mixed effect. We never lower blood-pressure for therapeutic purposes by depression of the heart, although this might be done by such drugs as aconite or chloral.

The peripheral resistance in the circulation is diminished by purgatives, massage, and rest, or by the employment of the vaso-dilators, such as nitrite of amyl or nitroglycerin. Vaso-constriction may be brought about by acting on the centre (caffeine, cocaine, and strychnine), by excitation of nerve-cells (coniine, nicotine, lobeline), excitation of nerve-endings (adrenalin, digitalis), or excitation of the plain muscle of the vessels (barium, lead, silver).

In the treatment of *shock* it is frequently necessary to raise blood-pressure immediately. Primary shock occurs at once after receiving a severe injury. The peripheral stimulus affects the centres in the medulla so that the respiratory and especially the vaso-motor centres lose their ordinary response to normal afferent stimuli. The splanchnic vessels dilate to an enormous extent and a profound fall in blood-pressure ensues.

Secondary shock comes on later : it is due to destruction of tissues and the absorption of their break-down products which have an action somewhat similar to that of histamine (see Ergot), causing great dilatation of the capillaries ; so that whether hæmorrhage has occurred or not there is a deficiency of blood. Deficient circulation means deficient oxygenation, and consequently an increase in the production of lactic acid and depletion of the alkali reserve—a condition we call " acidosis." Here, the administration of vaso-

constrictors is inadvisable because, although they raise pressure, they do this by constricting arterioles and diminishing the supply of blood to the organs in which there is an accumulation and stasis of blood in the capillary areas.

The following fluids are used in these conditions for transfusion directly into the circulation:—

1. **Iso or Hypertonic Saline.**—The water and saline leave the vessels in about half an hour and the blood-pressure returns to its former level.

2. **Ringer's Solution with Gum Arabic** (6 per cent.).—The gum provides the necessary viscosity and the blood-pressure is maintained.

3. **Transfusion of Blood.**—The blood of some people when mixed with that of others causes the corpuscles to clump or agglutinate, so that special donors must be chosen whose blood is harmless. The donor's blood may be transfused directly arm to arm; or it may be kept in an isotonic solution of dextrose and sodium citrate in the cold for use when required: the blood remains intact and retains vitality. The transfusion method is especially valuable in hæmorrhage and blood diseases such as pernicious anæmia.

MATERIA MEDICA

Hirudo (leeches).

The glands of the leech contain a deutero-albumose, hirudin. It is non-poisonous but prevents coagulation of the blood; 1 mgrm. prevents the coagulation of 20 c.c. blood almost indefinitely.

CHAPTER XII

ON CERTAIN DRUGS WHICH EXCITE SENSORY NERVE-ENDINGS

ACONITE. VERATRINE. STAVESACRE

ACONITE

Aconite Root, from *Aconitum napellus*, is the official variety of the Pharmacopœia. It contains three alkaloids, of which (1) aconitine is the most important, and to which the characteristic action of the crude drug is due. Many samples of German and other aconitine are made up of other less active alkaloids, and may contain little of the real aconitine. (2) Benzaconine, a very bitter and amorphous alkaloid, is obtained by the hydrolysis of aconitine. (3) Aconine is another alkaloid with a sweetish taste, which results from the still further hydrolysis of aconitine. Aconite root also contains aconitic acid.

ACTION

Externally the drug has a characteristic action on the sensory nerve-endings. If a minute trace is applied to the tongue it first produces a tingling sensation, followed by numbness and, later, anæsthesia. So characteristic is this action that it forms our most delicate test of the presence of small quantities of this alkaloid. If a trace of the alkaloid obtains entrance into the nostril, it excites the fifth nerve-endings and induces certain reflex effects, particularly violent sneezing, coughing, a large flow of mucus, and, in some cases, even vomiting. The drug is not absorbed from the unbroken skin, but if it is rubbed in with fat the typical tingling sensation is produced, and is followed subsequently by anæsthesia. It is therefore used as an ointment to relieve pain, such, for example, as that of neuralgia. It produces no redness or other signs of inflammation. Applied to the conjunctiva it acts as a local anæsthetic, but it is not used for this purpose, since it is absorbed.

Although aconitine, like the other alkaloids, is not absorbed from the unbroken skin unless it is rubbed in with chloroform, alcohol, or some fatty substance, it is readily taken up into the system from all mucous surfaces. Hypodermic injections are very painful on account of the initial stimulation of sensation.

After absorption one of the most characteristic effects of the drug

is again this excitation of nerve-endings. Even after hypodermic injections the characteristic tingling comes on after absorption, especially in the more sensitive parts, such as the tongue, throat, and finger-tips, and there is a scratching sensation in the pharynx. These affections may be examined subjectively, but there are others of which we can have no cognisance directly, but which, nevertheless, may have a very decided effect on certain functions. The sensory terminations of the vagi in the lungs are very active in producing reflex effects upon the heart, respiration, bronchioles, and other organs; and if these are excited, as we can hardly doubt they would be by aconitine, we have an explanation of many of the phenomena we shall presently describe. This action of the alkaloid has led to its use in some painful nervous diseases, especially in neuralgia of the fifth nerve. Aconitine also excites certain secretory nerve-endings, and so gives rise to a small increased flow of sweat: the salivation is not due to this cause, but is reflex, the result of stimulating the sensory nerve-endings in the mouth. Large doses frequently induce irregular fibrillary twitchings in striped muscle very similar to those seen after physostigmine. They can still be observed even after section of the motor nerve, but are removed by curare. So that, besides exciting the sensory endings, there is reason to believe that the motor nerve-endings are also affected, though to a minor degree only.

The **medulla** shows all the signs of excitation at first, and of depression later. In small doses, therefore, the *respiration* is increased in depth and frequency; but soon this gives place to a slower and more laboured type of breathing, and sometimes to marked dyspnœa. Some of these effects are, without doubt, reflex, arising from excitation of the sensory vagal endings in the lungs. But not all, for the dyspnœic type of respiration still obtains even when the vagi are cut, which suggests that there is either a direct effect on the medulla or an excitation of the broncho-motor nerve-endings. There is certainly some central depression, for death ultimately ensues from respiratory failure. The *heart-beat* is slowed either directly or reflexly through the centre; the slowing is not obtained if the vagi are previously severed. Aconitine is therefore used to slow the heart when a pure central inhibition is desired; the effect is associated with a fall in blood-pressure, and is especially marked in the quick heart of pyrexia. The *vaso-motor centre* is also excited, but the blood-pressure, after therapeutic doses, does not rise on account of the very decided cardiac inhibition.

It is doubtful if aconitine has any action on the higher parts of the brain, and the convulsive movements, which are sometimes seen late in poisoning, are asphyxial convulsions. This absence of action of the drug on any portion of the central nervous system except the medulla supports the view that the medullary effects are reflex and not central. For if the drug acted upon the centre directly,

then in big doses one would expect it to attack other parts of the brain, or the cord.

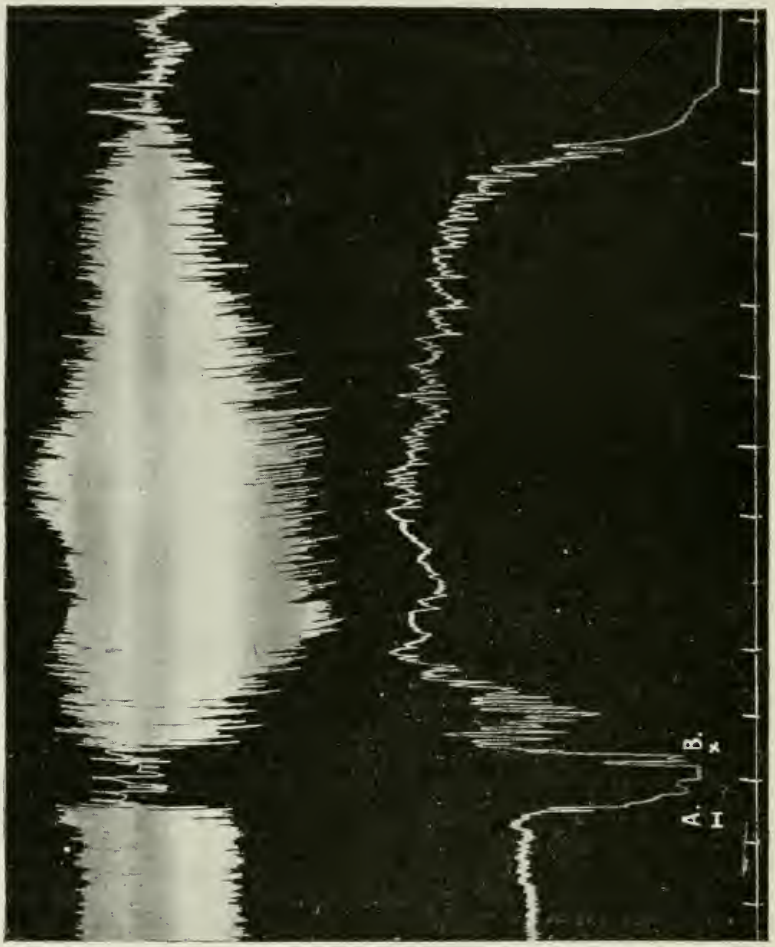


FIG. 53.—DOG. MOVEMENTS OF THE LEFT VENTRICLE. B.P.

The movements of the ventricle were recorded by attaching it to a thread passing over a pulley to a weighted lever. At A an injection of aconitine was administered by a vein. The heart stopped almost completely and blood-pressure fell. This is due to excitation of the vagal centre, because when the vagi are severed, one at B and the other a little later, the heart beats more rapidly than ever and blood-pressure bounds up. Later the action of aconitine on heart-muscle is shown. The heart beats much more vigorously and rapidly: the rate increases so much that the heart soon ceases to fill and empty properly, so that the output is diminished and blood-pressure falls. Finally, the muscle enters into fibrillary twitchings. Time = 10 secs.

On the **heart** and **circulation** aconitine produces a decided action. The type of change should be studied first in the frog in this animal the alkaloid induces a very short period of accelera-

tion, followed by a longer period of slowing. The slowing is vagal in origin, since it can be removed by the application of atropine. But, in any case, the heart soon begins to quicken again, irregular beats appear, one very characteristic effect being auricular-ventricular arrhythmia. In the later stages of this condition there may be arrhythmia in different parts of the ventricle, some parts contracting whilst others are dilating.

In mammals we have seen already that aconitine in therapeutic doses slows the heart. If the dose is increased, a second stage of acceleration occurs in much the same way as in the frog's heart: this effect is seen perfectly well in the isolated mammalian heart. As the acceleration increases, irregularity of rhythm appears, and in consequence there is considerable fluctuation in the blood-pressure. Stimulation of the vagus during this period often tends to make the heart more regular, and so raises the blood-pressure. In the later stages, when the auricular-ventricular arrhythmia is well developed, the vagus is entirely deprived of its control. This action is directly on the heart-muscle, and must, as in the case of caffeine, be referred to the excito-motor area. This we know because aconitine will still accelerate an isolated mammalian heart even when all nervous structures (vagus and sympathetic) have been paralysed by some drug such as apocodeine. Death of the heart occurs by the muscle entering into fibrillary twitchings (Fig. 53).

Aconitine is sometimes employed to reduce the **temperature** in fevers. It acts as a mild diaphoretic as we have seen, but the fall of temperature is probably due to some central effect. The drug is excreted mainly by the kidneys; traces have been discovered in the saliva. After hypodermic injections it has been detected in the stomach.

Symptoms.—Shortly after taking $\frac{1}{30}$ gr. of aconitine the characteristic tingling and numbness are felt on the tongue, lips, and mouth. This is followed by pain in the stomach, nausea, and sometimes vomiting and purging. The vomiting no doubt is due to a reflex from the stomach, and the purging is possibly a local reflex. Later the characteristic tingling spreads over the whole body. The patient is restless and fibrillary twitchings of the voluntary muscles appear. The skin becomes flushed, but a very characteristic "chilly sensation" occurs even before the temperature or the circulation through the skin is in any way altered, suggesting some effect on the nerves conducting the sensation of heat. Still later, the respiration becomes dyspnœic in character and the skin cold, livid, and covered with sweat. Death may occur from respiratory paralysis.

The heart, which was at first very slow, in the later stages becomes much quickened, and is probably in all cases the most dangerous symptom. Atropine very often greatly improves the condition of respiration: this may be due to its stimulant effect on the centre, but is more probably the result of paralysis of the vagal nerve-endings in the lung and hence the relief of broncho-constriction.

Benzaconine

This alkaloid is only about $\frac{1}{240}$th as toxic as aconitine. It slows the heart, especially the ventricular beat, like aconitine, but differs from it in that it induces a lethargic condition, and has no special effect on sensory nerve-terminations.

Aconine

Aconine is only one-ninth as toxic as benzaconine, and so, for practical purposes, it can be regarded as non-poisonous.

MATERIA MEDICA

Aconiti Radix.—Must contain not less than 0.4 per cent. of ether-soluble alkaloid.

Preparations

1. **Linimentum Aconiti.**—Must contain 0.2 per cent. ether-soluble alkaloid.
2. **Tinctura Aconiti.**—Standardised to contain 0.04 per cent. of the ether-soluble alkaloids.

Dose, 2 to 5 m. (12 to 30 centimils).

Aconitina.

Preparation

Unguentum Aconitinæ.—2 per cent.

VERATRINE

Veratrine is a mixture of several alkaloids obtained from *Cevadilla*. Chemically it is related to aconitine, since it is easily decomposed into angelic acid and cevine: the latter is closely related to aconitine. The veratrine of the Pharmacopœia consists of (1) veratrine, (2) cevadine, (3) cevadilline.

Action

(1) *An aconitine-like action on the nervous system.*

(2) *A specific action on all forms of muscle-tissue.*

Externally veratrine gives rise to tingling: this is followed by a sensation of numbness and coldness, which lasts for several hours. If a mixture of one part veratrine in five or six hundred parts of starch is sniffed up the nostril, it irritates the nerve-endings of the fifth, and induces sneezing, coughing, and an increased flow of mucus. Formerly it was used to fortify snuffs. The local anæsthetic action of veratrine has rendered it useful in certain forms of neuralgia. Unlike aconitine its local use is generally followed by some irritation. The ointment is used in some forms of neuralgia.

On **nerve-endings** veratrine acts after absorption in much the same way as aconitine. It induces tingling in the soft palate and pharynx, and reflex salivation; and if the drug is given hypodermically there is burning pain followed by numbness at the seat of injection. Salivation and sweating are both profuse. In the frog the motor nerve-endings are paralysed by big doses, but it is difficult to induce this effect in mammals. Veratrine in the frog has the remarkable property of traversing long stretches of nerve even when the circulation has stopped, so that if it is applied locally to a nerve it may pass along and reach central portions of them.

Upon the central nervous system veratrine produces little effect. Respiration is accelerated at first, and this is followed by slowing and a spasmodic type of breathing. The initial acceleration may be due to the stimulation of the sensory endings in the lungs, but the dyspnœic type of respiration which develops later is due to broncho-constriction, the effect of the drug directly on the muscle-fibre of the bronchioles.

The most characteristic effect of veratrine is on **muscle**. All forms—striped, plain, and cardiac—are affected in much the same way, and the action consists in an increased irritability and a greater power of doing work. On *striped muscle* veratrine increases the contractility, so that, with the same stimulus, the height of contraction is greater than before. To a muscle suffering from fatigue it restores the contractile power. Its irritability is so increased that the muscle reacts to weaker stimuli, and the total work obtainable is augmented. If veratrine is injected into a mammal or frog the animal is still able to contract its muscles with its accustomed rapidity, but the relaxation of these is so slow that it cannot recover its former position for some seconds. These effects can be demonstrated on the isolated muscle of the frog: stimulation of a veratrinised muscle produces a bigger contraction than normally, and the relaxation is long drawn out, to twenty or thirty times the normal, and usually exhibits slight undulations. The whole contraction lasts from five to ten seconds. This is not an effect on the central nervous system, since it can be produced in an isolated muscle; nor is it a tetanus, because if the nerve of a normal nerve-muscle preparation is placed upon the muscle of a second veratrinised nerve-muscle preparation, and if the latter is induced to give one of its typical contractions, the normal muscle produces a simple twitch. If the veratrine contraction were a tetanus the normal muscle would also record a tetanus.

We regard the action as due to increased katabolism. If we consider a simple muscle contraction as due to the explosion or setting free of some chemical substance in the muscle-biogen, then veratrine may be regarded as a substance which increases the supply of this explosive body; so that when a stimulus comes which initiates the explosion so much material has collected that the contraction is prolonged. If this interpretation be correct, each

successive stimulus to the muscle should be followed by a quicker relaxation until, after a time, the normal is reached, and this is what occurs. It is also easy to explain how cold, or drugs which directly depress muscle-fibre, such as potassium, can act like fatigue in antagonising the veratrine-effect.

On *plain muscle* veratrine increases the tonus and, to a less extent, the automatic movements. Vomiting results reflexly from the violent movements obtaining in the alimentary canal. The stomach and intestines are more contracted than usual, and intense colicky spasms occur from time to time: the effect closely resembles that of barium and lead, and is not analogous to the true increased peristalsis characteristic of the vegetable purgatives. Both the tonus and peristaltic waves of the uterus are increased; and in the pregnant condition abortion may occur. The bladder, bronchioles, spleen, and all other forms of plain muscle are affected similarly. Veratrine induces intense vaso-constriction. The action is directly on the muscle-fibre, since the pulmonary, coronary, and cerebral vessels, which contain few or no vaso-motor nerves, are also constricted during perfusions. Its action in this respect is in marked contrast to that of pilocarpine and adrenalin.

The effect on the heart may be studied first in the frog. The systole is increased not only in strength but in duration, and diastole is diminished, so that, as the action develops, the tonus of the ventricle becomes greater and greater, and its relaxation less and less, until at length the heart stops in systole. The mammalian heart is similarly affected: the rhythm is at first slowed a little, due to some medullary effect, but this soon gives way to quickening. The force of systole is increased, and the heart does not relax so perfectly as before. The total result of this on the heart is to increase the output of blood per minute. Blood-pressure rises mainly on account of the vaso-constriction, but partly because of the cardiac effects.

Symptoms.—Symptoms of poisoning by veratrine are characterised by a severe burning and tingling sensation in the mouth, followed by numbness. This is succeeded in about half an hour by pain in the abdomen, vomiting, violent colic, and sometimes purgation. The respiration is asthmatic in character, and the pulse, at first slow and irregular, later becomes considerably quickened. The prolonged relaxation and fibrillary contractions of the muscles occasionally form a typical picture. Generally, death results from collapse.

MATERIA MEDICA

Veratrina. **Dose,** $\frac{1}{10}$ **to** $\frac{1}{16}$ **gr.** (Not official.)

Amyl Colloid. (Not official.) Amyl hydride, aconitine, veratrine, collodion. It is used to paint on tender spots in neuralgias.

STAVESACRE

Stavesacre seeds are the dried seeds of *Delphinium staphisagria*. They contain four alkaloids, delphinine and staphisagrine being the most important. About 27 per cent. of fixed oil is also present.

Delphinine acts in the same way as aconitine, and is about equally toxic. When it is rubbed into the skin over painful areas or over nerves, it produces first tingling and later numbness, and the pain is relieved. It is therefore sometimes employed as an ointment in neuralgias. The ointment is principally used to destroy the pediculi of the head; the official preparation does this with safety.

Internally delphinine acts on the respiration and heart like aconitine, and was employed at one time as an emetic and vermifuge. Staphisagrine acts like curare, and so tends to antagonise the fibrillary contractions produced by delphinine.

MATERIA MEDICA

Staphisagriæ Semina.

PREPARATION

Unguentum Staphisagriæ.—20 per cent. crushed seeds, yellow beeswax, benzoated lard.

CHAPTER XIII

DRUGS ALTERING THE CALIBRE OF THE VESSELS

Vaso-constrictors.—The plain muscle of the blood-vessels can be affected by drugs in the same way as any other plain muscle. The vessels which are especially liable to alterations in calibre are the small arterioles; the larger arterioles, the veins and the capillaries undergo but little change. The arterioles are always in a condition of some tonus, which is partly the result of central activity and is partly peripheral.

Vaso-constriction may be brought about in one of the following manners:—

(1) Stimulation of the centre in the medulla. (*a*) Reflexly by stimulation of any sensory nerve (blisters). (*b*) Excess of CO_2 in the blood (asphyxia). (*c*) Drugs: strychnine, ammonia, caffeine, atropine, cocaine, digitalis, aconitine, prussic acid, &c.

(2) Stimulation of sympathetic nerve-cells:—Nicotine, coniine, lobeline. The stimulation in the case of these three is only transient, the ultimate effect being depression.

(3) Stimulation of the peripheral nervous mechanism:—Adrenalin.

(4) Direct action on plain muscle:—Digitalis, barium, veratrine.

The arterioles in various organs of the body contain relatively different amounts of muscle, and also differ in their innervation, and in correlation with this fact one would not expect them to be all affected in quite the same way by drugs. Thus, the splanchnic vessels are well supplied with both nerves and muscles, and are capable of greater alterations in volume than other vessels in the body, so that the injection of such a drug as adrenalin, which produces intense constriction of these vessels and a big rise in blood-pressure, may actually dilate the limb-vessels by the increased pressure, in spite of their own tendency to contract with the stimulation of the drug. The lung and brain vessels contain no vaso-motor nerves of significance, and are but poorly supplied with muscle, so that in whatever way blood-pressure is raised, these organs behave passively and dilate.

The effects of vaso-constriction of peripheral origin will, therefore, be:—(1) A rise in general blood-pressure; (2) congestion of the lung and brain vessels; (3) slowing of the heart from reflex stimulation of the medulla; (4) some stimulation of respiration. Such drugs would obviously be indicated in "shock" and

'collapse," and in narcotic poisoning where the blood-pressure is low from depression of the vaso-motor centre.

Vaso-dilators are drugs used to dilate the peripheral arterioles. They act in one of three ways :—

(1) By depression of the vaso-motor centre in the medulla, *e.g.* narcotics, chloral, &c. ; (2) by depression of sympathetic nerve-cells : apocodeine, codeine, apomorphine, coniine, nicotine ; (3) by depression of plain muscle : theobromine, nitrites, and organic nitrates.

When an organ enters into a state of activity its blood-supply is increased : the mechanism by which this is brought about may be either reflex or due to metabolic products liberated during the activity of the organ. If the dilatation is at all extensive blood-pressure tends to fall, and this reflexly causes certain vessels elsewhere to constrict, and the heart to beat more rapidly. For example, we know that the abdominal vessels dilate during digestion, and this is associated with vaso-constriction of the skin-vessels.

We have noted already that stimulation of any sensory nerves, such, for example, as may be affected by a blister, increases the blood-pressure mainly by vaso-constriction, and accelerates the heart. This blood must find a haven somewhere ; some of it may pass to the limbs, but the bulk tends to fill the veins and the vessels of the lungs and liver.

If a sensory stimulus is very prolonged and intense, and more especially if it is visceral in origin (such as may be brought about by a drug which produces gastro-enteritis), then enormous vaso-dilatation is produced, especially in the splanchnic area. Practically all the blood goes to the abdomen, the blood-pressure falls very low, and although the heart may be acting well, it beats to no purpose. This condition we speak of as collapse, and it is probably identical with surgical shock.

The drugs especially used in medicine to lower pressure are the following :—

Amyl nitrite, obtained by the action of nitrous acid on amyl alcohol, and distilled at about 130° C., is a yellowish ethereal liquid composed of a mixture of nitrites, in which iso-amyl nitrite largely preponderates. It is almost insoluble in water, and deteriorates on exposure to air. The drug is contained in glass capsules, which can be crushed in a handkerchief when required.

Sodium nitrite, $NaNO_2$, a deliquescent powder very soluble in water, obtained by fusing sodium nitrate with metallic lead, and hence it often contains a trace of lead.

Nitroglycerin, $C_3H_5(NO_3)_3$, is a nitrate, but is readily converted into nitrite in the body.

Liquor trinitrini, a 1 per cent. solution of nitroglycerin in strong alcohol. When mixed with more than its own volume of water opalescence should appear (precipitation of nitroglycerin) ; this forms a rough test as to the quantity of the drug present.

Liquor ethyl nitritis, a 3 (or not less than 2.5) per cent. solution of $C_2H_5.NO_2$, dissolved in a mixture of 95 parts absolute alcohol and 5 parts of glycerin.

Spiritus etheris nitrosi (sweet spirits of nitre) is a limpid faintly yellow inflammable liquid. It is an alcoholic solution containing $C_2H_5NO_2$, $CH_3.COH$, and small amounts of other substances. Ethyl nitrite must be present from 1.5 to 2.0 per cent.

Erythrol tetranitrate, soluble in 1 in 50 absolute alcohol.

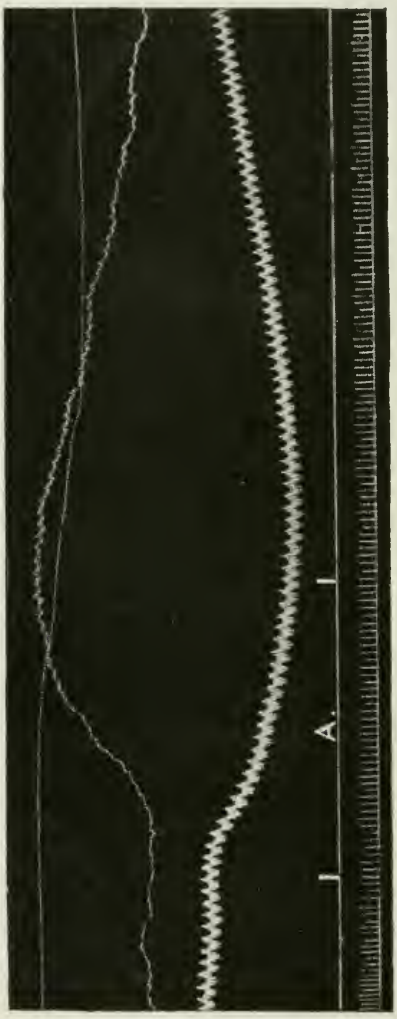


FIG. 54.—CAT. LIMB-VOLUME, INTESTINAL VOLUME, AND BLOOD-PRESSURE. Between the indicated marks at A, amyl nitrite was given by inhalation. The intestinal vessels dilated and the blood-pressure in consequence fell. The limb-vessels also tend to dilate, but most of the blood is in the splanchnic area, and as there is not sufficient to fill them the volume of the limb actually diminishes. During recovery the splanchnic vessels constrict and the blood-pressure gradually rises. Time = secs.

ACTION OF NITRITES IN GENERAL

Plain Muscle.—The principal action of the nitrites is on every kind of plain muscle throughout the body, which becomes gradually paralysed; this action is most strongly marked on the blood-vessels. If a saline solution containing 1 in 10,000 of sodium nitrite is perfused through the vessels of a tortoise, the outflow from the vein is increased by nearly 20 per cent., and 1 in 1000 parts perfused through a sheep's kidney doubles or trebles the flow. This effect, which is produced by all nitrites, must be located either on the peripheral nervous mechanism or on the muscle. The effect is upon the plain muscle directly, because the lung-vessels markedly dilate when artificially perfused, and these contain no vaso-motor nerves (Figs. 54 and 56).

Other forms of plain muscle also relax, and this can be readily

shown in the case of the ureter, intestines, and bronchioles, but the effect is never so decided as that on the vessels. Nitrites are, therefore, employed in spasmodic conditions of plain muscle, as, for example, in asthma, hepatic colic, and renal colic.

Striped muscle is similarly affected by nitrites, but to a lesser degree than the plain. The contractility and vitality of a frog's gastrocnemius are rapidly impaired by a solution of 1 in 5000 sodium nitrite, and, after about two hours' immersion, it no longer responds to electricity. The effect is directly on the muscle, for excitation of the nerve will always give as good a contraction as direct stimulation of the muscle.

Circulation. — The blood-pressure falls very decidedly, and entirely as a result of the vaso-dilatation. If a drop or two of amyl

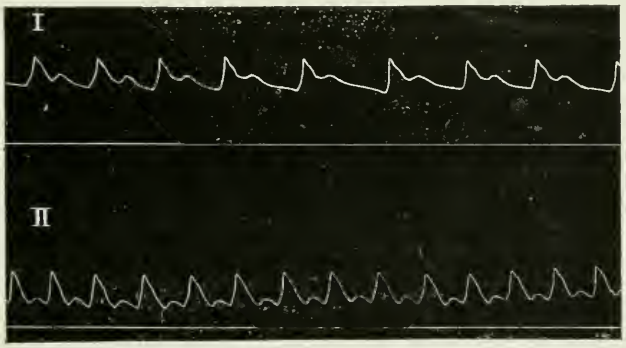


FIG. 55.—SPHYGMOGRAPH TRACING FROM A MAN.

I = normal. II = after an inhalation of amyl nitrite. The heart-beat is quicker, and blood-pressure is lower. Note the pronounced character of the dicrotic notch. The time is the same throughout.

nitrite be inhaled by a man, in a few seconds the face flushes, the carotids throb, the heart beats more rapidly, and there is a feeling of fullness and throbbing in the head (Fig. 55). Larger inhalations produce giddiness and stupor. On the skin the vaso-dilatation is most noticeable over the "blush area," an area which has a special innervation: atropine and other drugs may decidedly dilate the vessels of this area without greatly affecting those of the rest of the skin.

It was considered formerly that some of the vaso-dilatation was due to depression of the medulla, but this is not probable in view of the fact that amyl nitrite injected up one carotid directly into the brain stimulates the medulla and produces a rise in blood-pressure. Such depression of the medulla as occurs is the result and not the cause of the fall in blood-pressure. The vaso-dilatation affects both the arterioles and also, though to a much smaller degree, the veins; the blood is stored up mainly in the splanchnic area.

Heart.—The nitrites quicken the heart. This effect is caused by the fall in blood-pressure whereby the normal tonic influences of the medulla are diminished. The effect is just the reverse of that which obtains when the blood-pressure is raised: in this case the heart is slowed by the stimulation of the medulla resulting from the increased pressure.

If the vaso-dilatation is sudden, as after an inhalation of amyl nitrite, the heart may be quickened by twenty or thirty beats per minute; the reflexes from the vessels and the physical effects will aid in this acceleration.

If the isolated frog's heart be perfused with a 0.0001 per cent. solution of nitrite it becomes quicker and slightly weaker, but there is no other effect. The heart of the mammal is not influenced directly by medicinal doses of the nitrites. But larger doses weaken the beat and diminish the output by depressing cardiac muscle in much the same way as any ordinary plain muscle. Therefore, nitrites in small medicinal doses only affect the heart indirectly through the physical alterations of the circulation.

Blood.—If sodium nitrite is mixed with blood outside the body in the proportion of 1 to 10,000, in a few hours methæmoglobin appears, and if the proportion is 1 in 1000, methæmoglobin appears in two or three minutes (Fig. 69). In man very little of the oxyhæmoglobin can be so transformed, because, even after excessive or poisonous doses of nitrites have been administered, the spectroscope shows no evidence of methæmoglobin. The blood-corpuscles are not destroyed as they are with most other methæmoglobin-formers, and the methæmoglobin is gradually re-converted to oxyhæmoglobin by contact with the tissues.

The significance of the production of methæmoglobin in any considerable amount depends on its inability to act as an oxygen-carrier, and so in the living animal cyanosis and asphyxia occur. But there is no fear of any such action when the nitrites are used medicinally.

Other Effects. — Moderate doses slightly increase both the secretion of sweat and urine owing to vascular changes; the dilatation of the skin-vessels is also responsible for a small fall in temperature by facilitating the heat loss. Respiration becomes slightly quicker and deeper, especially in the rabbit (Fig. 56).

Excessive doses given by the stomach upset digestion, and, after absorption, may produce asphyxial convulsions. The confusion and affection of sight are the result of circulatory changes in the brain and eye respectively.

Excretion. — Nitrites undergo partial oxidation, and appear in the urine both as nitrates and nitrites, but the amount excreted does not equal the amount absorbed, so that some is apparently still further broken up: amyl nitrite is excreted in the same way, the amyl radicle being completely absorbed.

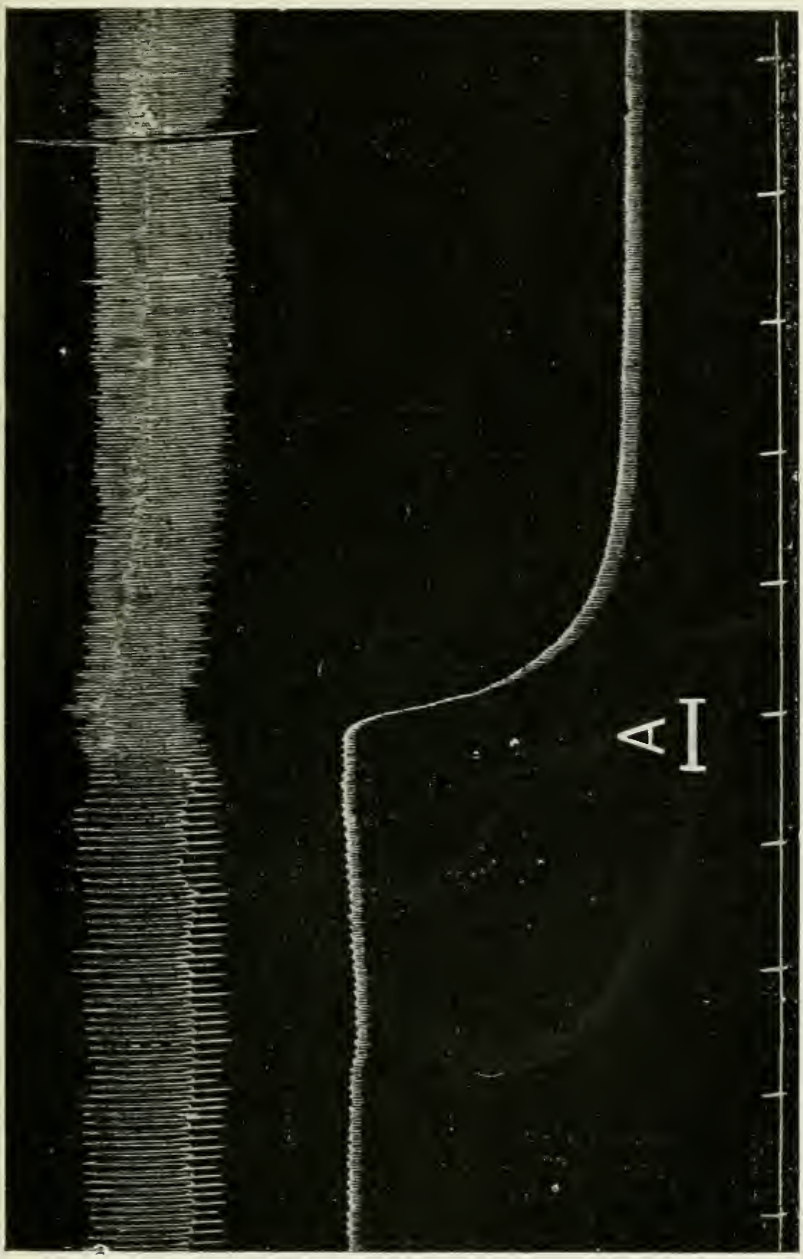


FIG. 50.—RABBIT. RESPIRATION AND BLOOD-PRESSURE.

At A a small injection of amyl nitrite was made into a vein. The respiration (upstroke = inspiration) and heart-beats became quicker, and blood-pressure fell. The strength of the pulse was not diminished. Time = 10 secs.

Differences in Action of the Members of this Series. — The difference in action between the various members of this group is dependent on rate of absorption and the ease with which nitrite is set free in the blood. *Amyl nitrite*, when inhaled, is absorbed almost immediately by the great area of lung-vessels, and its action is correspondingly quick, but it rapidly passes off as the nitrite is either excreted or oxidised to nitrate. By the stomach it is much less active, as nitrous acid is formed which decomposes immediately. When injected it also acts more slowly than by inhalation, and produces glycosuria.

Sodium nitrite is administered by the mouth, and therefore acts more slowly than amyl nitrite, but the effect lasts much longer. A little of it is converted to nitrous acid (HNO_2) in the stomach, and gives rise to gastric irritation: this prohibits its general use.

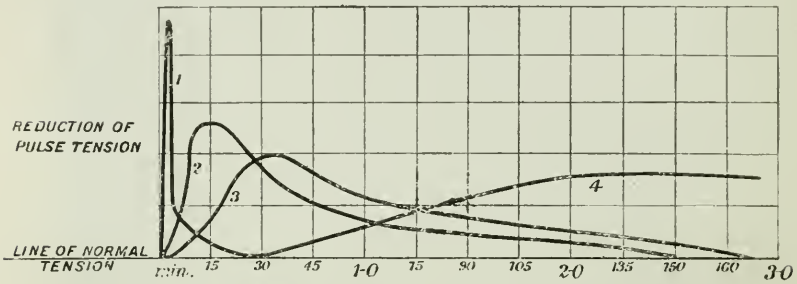


FIG. 57.—DIAGRAMMATIC REPRESENTATION OF THE CONDITION OF THE VESSELS AFTER THE EXHIBITION OF VARIOUS NITRITES.

The ordinate represents degree of dilatation, and the abscissæ, time in minutes. 1 shows the effect of an inhalation of amyl nitrite—the effect is intense but transitory. 2 shows the effect of nitroglycerin, 3 of sodium nitrite, and 4 of erythrol tetranitrate. The last body is so slowly absorbed into the system that the effect is prolonged over a long time. The degree of vaso-dilatation was gauged by the fall in blood-pressure (Bradbury).

After injection into a vein, 50 per cent. can be recovered from the urine; the rest is mainly oxidised to nitrate.

Liquor trinitrini (nitroglycerin), $C_3H_5\{^{NO_3}_{NO_3}_{NO_3}$, is a nitrate. When administered by the mouth it has a very rapid action, beginning almost immediately; the vessels reach their maximum dilatation in four or five minutes, and the main effect is over in twenty minutes. It is absorbed unaltered by the stomach, and is supposed to be decomposed within the body to nitrite. Even $\frac{1}{100}$ gr. produces marked dilatation of vessels, but enormous doses may be taken without serious harm.

Liquor ethyl nitritis has an action much the same as that of sodium nitrite.

Spiritus etheris nitrosi contains about 2 per cent. ethyl nitrite. It is largely used as a mild diaphoretic and diuretic.

Erythrol tetra-nitrate (not official) is a very insoluble substance,

and is absorbed very slowly; therefore, a mild dilatation over a prolonged period is obtained. The maximum dilatation occurs in from two to three hours.

MATERIA MEDICA

Amyl Nitris. Dose, 2 to 5 m. (12 to 30 centimils) as an inhalation.
Nitroglycerinum. Dose, $\frac{1}{200}$ to $\frac{1}{50}$ gr.

PREPARATIONS

1. **Liquor Trinitrini.**—1 per cent.
   Dose, $\frac{1}{2}$ to 2 m. (3 to 12 centimils).
2. **Tabellæ Trinitrini.**—Nitroglycerin, each containing 0.5 milligram.
   Dose, 1 or 2 tablets.

Sodii Nitris. Dose, 1 to 2 grs. (3 to 12 decgrms.).
Liquor Ethyl Nitritis. Dose, 15 to 60 m. (1 to 4 mils).
Spiritus Etheris Nitrosi. Dose, 15 to 60 m. (1 to 4 mils).
Erythrol Nitras. (Not official.) Dose, $\frac{1}{2}$ to 1 gr. (2 to 6 decgrms.).

BARIUM

Barium is a powerful poison, having a special affinity for all forms of muscle. As soon as this drug comes in contact with

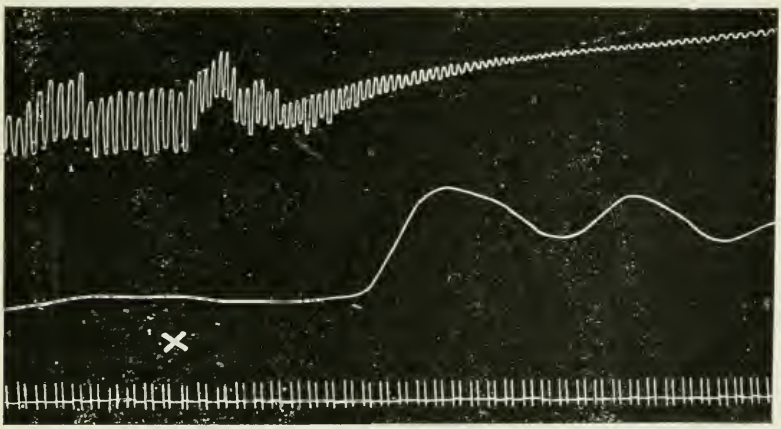


FIG. 58.—FROG (PITHED). MOVEMENTS OF THE HEART AND STOMACH.

The stomach was filled with water and connected to a manometer, the movements of the fluid in which are here recorded; so that when the stomach contracts the fluid rises in the manometer and the record goes up. At the X $BaCl_2$ was injected into the hepatic vein. The heart is shown to die in systole. The stomach, which before injection showed no movements, enters into tonic contraction and a series of waves is produced. Time = secs.

muscle-fibre, whether it be by direct application or through the circulation, it throws the muscle into tonic contraction; and so constant is this effect that barium can be employed as a test for the presence of muscle-fibre in a tissue.

When barium chloride is taken by the mouth it produces violent colicky pains, nausea, vomiting, and diarrhœa, all these effects being due to the action of the drug on the plain muscle of the gut. Death is caused by paralysis of the central nervous system, and is preceded by violent tonic and clonic convulsions. The best antidote is sodium sulphate. Barium sulphate is used as a substitute for bismuth salts in X-ray work. Barium is mostly excreted by the gut.

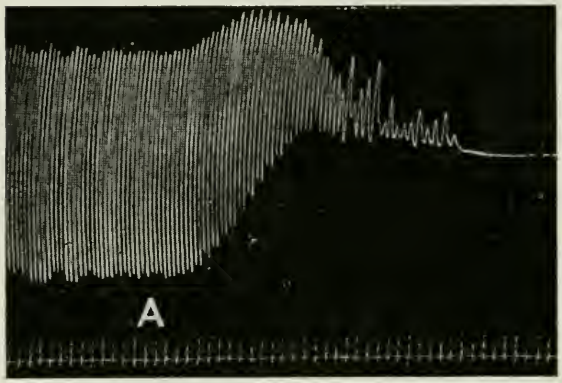


FIG. 60.—RABBIT'S HEART PERFUSED WITH RINGER'S SOLUTION.

At A a solution of 1 in 200 barium chloride was given and death occurred in systole.

ACTION OF DRUGS ON STRIPED MUSCLE

It is convenient at this point to classify the drugs acting on striped muscle:—

(1) There are those which diminish the power of the muscle to do work, and usually also the muscle-irritability. This effect can be obtained by such drugs as quinine, chloral, chloroform, potassium, lithium, and ammonium. In the living mammal they are not of much significance, since this effect is always overshadowed by other actions.

(2) There are those which increase the power of the muscle for doing work, such as the purine derivatives, veratrine and alcohol. This group is more important than the former, since these effects can be determined in the living animal. Some of these drugs, such as veratrine and barium, increase the contraction curve, as we have already seen; but this effect is only observed after poisonous doses, and can be obtained equally well with a host of other drugs which, administered in medicinal doses, produce no effect on muscle. As examples of other drugs which produce this veratrine-like action we may cite calcium, digitalis, squill, oxycolchicine, glycerin, and even normal saline solution made up with distilled water, *i.e.* containing no calcium salts.

(3) The third group consists of drugs which increase the irritability of muscle. Physostigmine, guanidine, and perhaps aconitine, are amongst the members of this group; they find no use for this purpose in therapeutics.

Guanidine does not occur in the animal body, but guanidine substitutes are among the products of protein metabolism, and methyl-guanidine is a normal constituent of muscle. Guanidine injected into animals causes twitchings of muscle like those of physostigmine, and like them can be controlled by injection of calcium salts. Large injections cause a curare-like paralysis. Guanidine is the exciting cause of the disease tetany. (*See* under Parathyroids.)

Many other drugs in large quantities affect muscles when applied directly, but they have no such action when given by the mouth. Thus, copper, zinc, saponins, lead, emetine, and cocaine all produce depression and death of muscle-fibre on direct application, but in the dosage in which they can be used in medicine they have not this effect.

CHAPTER XIV

ERGOT

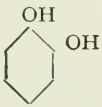
ERGOT is the compact mycelium of the fungus *Claviceps purpurea*, which develops in the ovary of the rye. It is not only an important remedy in practical medicine, but wide-spread epidemics of disease have resulted from eating bread made of rye which has been infected with the fungus.

The chemistry of ergot is not yet certain. It seems clear that during the growth of the fungus in the rye the proteins of the latter are broken down and bodies are formed to which the ergot owes its pharmacological activity. Three of these bodies require attention.

(1) *Ergotoxine*, $C_{35}H_{41}N_5O_6$, is a complex alkaloid with feebly basic properties soluble in alcohol but insoluble in water. It is the hydrate of the comparatively inert crystalline base ergotinine. The sphacelinic acid of Kobert and the sphacelotoxin of Jacobi, both impure substances, have actions similar to ergotoxine, and should be regarded as impure specimens of this alkaloid.

(2) *Tyramine*, or p.-hydroxyphenyl ethylamine, is one of a number of bodies derived from amino-acids during putrefaction of animal matter by the elimination of carbon dioxide. Tyramine is obtained by the splitting off of carbon dioxide from tyrosine; it is closely related, both chemically and pharmacologically, to adrenalin and hordenine of malt.

Tyramine.



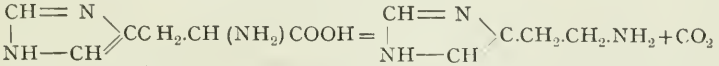
Adrenalin.

Hordenine.

Tyramine is soluble in alcohol and in about 95 parts of water.

Like adrenaline, it also occurs in the Animal Kingdom, and is the active substance in the poison glands of some cephalopods.

(3) *Histamine* or β-iminazolylethylamine can be obtained from histidine through the agency of putrefactive organisms just as tyramine can be obtained from tyrosine.



Histidine. Ergamine or Histamine.

It is soluble in water and alcohol.

Agmatine, first found in herring roe, is yet another amino-acid

derivative in ergot : in this case it is formed from arginine by the elimination of carbon dioxide. Its pharmacological action resembles that of ergamine, but is much weaker. Other constituents of ergot are choline, iso-amylamine, cadaverine, putrescine, but in amounts insufficient to produce any decided effect. Ergot also contains about 30 per cent. fixed oil.

The term *ergotin* is usually applied to the purified extract and not to any definite proximate principle. It is not advisable in the present state of knowledge to use these principles because clinical experiments have not yet defined their relative merits. The best plan is to prescribe a properly standardised preparation of the drug, and for the present this standardisation must be physiological, since the chemical process is not practical. Nevertheless, before describing the action of an ergot preparation, presumably containing all the active constituents, it will be advantageous to examine the effect of each important constituent, and, if possible, give to it its proper position when considering the action of the crude drug.

Ergotoxine is the active constituent of ergot, which induces gangrene : this substance in an impure form represents the sphacelotoxin of Jacobi. Ergotoxine increases the tonus and peristaltic movements of most plain muscle throughout the body. This effect is particularly marked on the vessels ; these become intensely constricted, and stasis occurs in parts of the peripheral circulation. The vaso-constriction is associated with the pouring out of a hyaline substance, which more or less completely blocks up the smaller vessels and results in peripheral gangrene : the walls of the larger arteries thicken and the lumen is diminished. In some animals, including man, gangrene of certain peripheral parts of the body results from this limitation of the blood-supply. In man the nose, ears, fingers, and toes are affected first ; in hogs the tips of the ears become black and fall off, and the skin sometimes shows local patches of gangrene as a pustular eruption. In fowls the gangrene is very easy to observe, and first affects the comb and wattles. Ecchymoses and ulceration of the alimentary canal, the result of vascular stasis, have also been observed in animals.

Other plain muscle is similarly affected, thus the movements of the alimentary canal are augmented, the uterus is thrown into tonic contraction, and, if gravid, abortion may be induced. The output of blood from the heart is increased on account of the augmented force of the cardiac contractions, and this also serves to raise blood-pressure. Ergotoxine depresses the central nervous system, and in large amounts produces complete paralysis.

The action of ergotoxine corresponds to an excitation of the cranial and sacral autonomic, and also of the true sympathetic nerve-supply to all organs containing plain muscle. The drug probably acts at the periphery, in spite of the fact that its direct application to an isolated tissue does not induce the typical effect; for example, no constriction results from its perfusion through

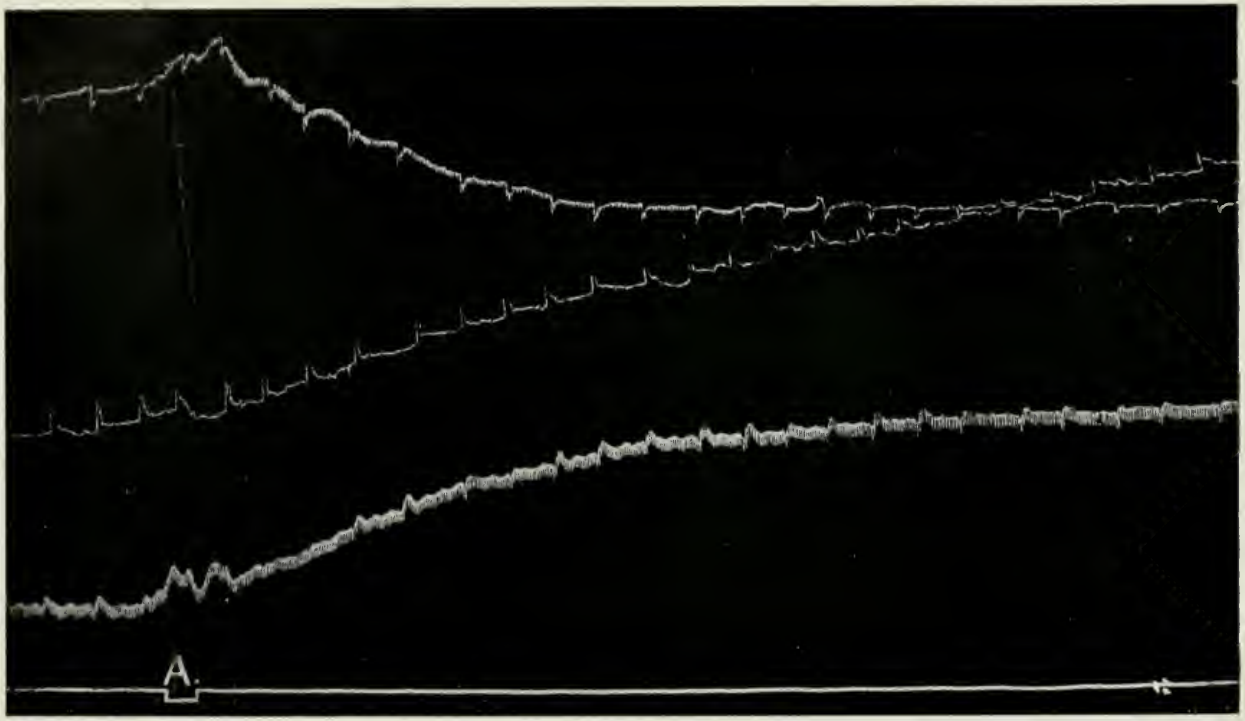


FIG. 61.—CAT (PITHED). ACTION OF ERGOT ON VESSELS.

The curves from above downwards represent (i) intestinal volume, (ii) limb-volume, (iii) blood-pressure. At A 6 m. of the liquid extract of ergot were injected into one jugular vein. The splanchnic vessels constrict, and largely as a result of this, blood-pressure rose. The limb-volume increased, because the rise in pressure more than counterbalances the tendency of the limb-vessels to constrict.

isolated vessels. The effect of ergotoxine is not essentially changed by destruction of the brain and cord, but it is entirely abolished by a dose of nicotine, apocodeine, or other drug, which paralyses sympathetic nerve-cells. In other words, after such a dose of nicotine, ergotoxine produces no rise of blood-pressure and no increased movements of plain muscle generally. Adrenalin and pilocarpine, which act more peripherally than the ergot, still induce their typical reactions. Poisonous doses of ergotoxine paralyse the motor-endings of the sympathetic.

Tyramine.—This base exerts an action throughout the body which corresponds to a stimulation of the sympathetic nerves and which resembles closely the effects of adrenalin, but differs from that substance in that it can be administered either subcutaneously or by the mouth without undergoing rapid destruction, and so produces its specific action. Adrenalin, on the contrary, is usually destroyed locally when given by either of these methods, so that its general specific effects are in most instances absent. The principal action of tyramine will therefore be shown on the heart and arterioles: the blood-pressure rises from vaso-constriction due to stimulation of the sympathetic nerve-endings, and the heart beats quicker and more vigorously for the same reason. The whole of the increase of blood-pressure resulting from an administration of the watery extract of ergot (extractum ergotæ liquidum) must be due to this substance, since ergotoxine, the other pressor substance in ergot, is absent from this preparation.

Tyramine causes increased uterine contractions, and this effect is much more pronounced when the uterus is gravid ; in some animals either no effect or inhibition may be induced in the non-pregnant condition. This is explained by the fact that the sympathetic supplies both motor and inhibitory nerves to the uterus, and the action of tyramine is the mean of the two effects. Apparently when the uterus hypertrophies during pregnancy the development of the motor sympathetic fibres overshadows that of the inhibitory, and so whilst in the pregnant condition tyramine causes very decided increase in the uterine contractions in the non-pregnant state, the effect is insignificant.

Tyramine is oxidised in the body to p.-hydroxyphenyl acetic acid.

It is of interest to note that tyramine is produced from the putrefaction of tyrosine in the human alimentary canal, and the absorption of large amounts might lead to pathological changes.

Histamine.—The characteristic effect of this base is its direct stimulant action on certain forms of plain muscle, in which both the automatic contractions and tonus are increased. This effect is especially marked on the uterus, for which histamine has a specific affinity, and its action upon this organ differs from that of tyramine, adrenaline, or ergotoxine in that the effect is as marked in the non-

pregnant as in the pregnant condition. The effect upon the plain muscle of the bronchioles is also distinct, but other forms of plain muscle, such as that in the heart, intestines, and bladder, are less influenced.

The peripheral arterioles tend to constrict, but the capillaries undergo wide dilatation, so that histamine induces a profound fall

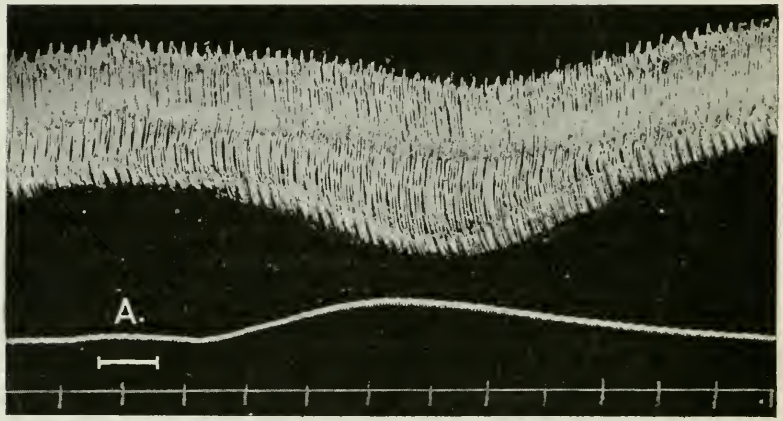


FIG. 62.—CAT. CARDIOMETER. BLOOD-PRESSURE.

At A 5 m. of extractum ergotæ liquidum were injected into one jugular vein. Cardiac systole (downstroke) and output (total height of curve) immediately began to increase; as a result the blood-pressure rose. As the effect passed off, the reverse conditions obtained. Time=12 secs.

in the systemic blood-pressure, though the pulmonary blood-pressure rises. Histamine exerts its action entirely at the periphery, and directly on muscle tissue.

An alcoholic extract of the intestinal mucosa has an action very similar to histamine. The name "vaso-dilatin" has been given to this hypothetical substance, which is almost certainly histamine.

The following table shows the action of the three main constituents of ergot on the vessels and uterus:

	SEAT OF ACTION.	BLOOD-VESSELS.	UTERUS.
Ergotóxine .	Peripheral nervous system.	Constriction (leading to gangrene). + B.P.	Contracts if pregnant.
Tyramine. .	Peripheral "nerve-endings." (β)	Constriction. + B.P.	Contracts if pregnant.
Ergamine or Histamine	Some portion of the muscle.	Wide dilatation of capillaries. - B.P.	Very decided contraction in all states, principally of a tonic nature.

Action of Crude Ergot.—Ergot is easily absorbed, and the various constituents on reaching the blood exert their specific effects on plain muscle throughout the body.

The peripheral *arterioles* constrict: this is partly due to the action of ergotoxine on the peripheral nerves and partly to the tyramine on the nerve-endings, but any vaso-constriction caused by the liquid extract must be due to tyramine since ergotoxine is not present. Ergamine dilates capillaries, but in the ordinary galenical preparations of ergot this dilator effect is overshadowed by the other constituents and vaso-constriction results (Fig. 61).

The *heart*, contrary to what is generally stated, is decidedly and directly influenced by ergot: it beats more vigorously, its systole is more complete, and its output is very considerably

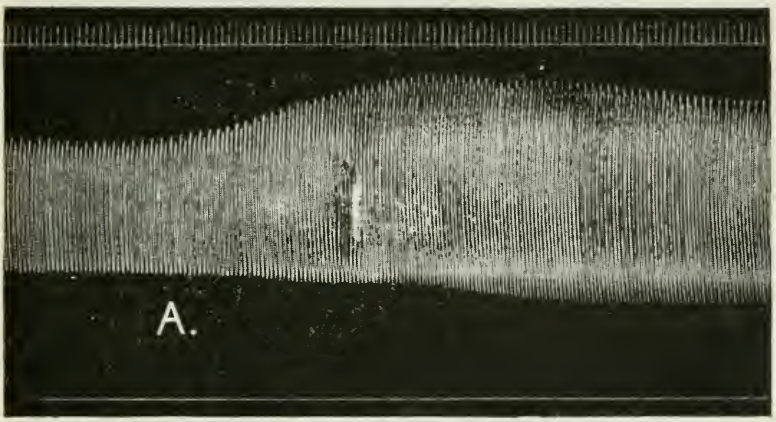


FIG. 63.—RECORD OF RABBIT'S HEART PERFUSED WITH RINGER'S SOLUTION, BY THE METHOD OF LANGENDORFF.

The upstroke represents systole. At A a minute amount of ergot was added to the perfusing fluid. The force of systole increased considerably, but the rate of beat was not much altered. Time = secs. Strength of Extract = 1 in 1000.

increased. This effect is easily shown on the living animal by recording the actual pull of the ventricle by suitable levers, or measuring the outflow of the blood during each beat by means of the cardiometer (Fig. 62). But it can be shown even better on the isolated heart perfused by a Ringer's solution. Here, as soon as the ergot reaches the coronary vessels, the heart begins to beat much more powerfully ; indeed, the effect is very like that of adrenalin, but differs in that there is not so much acceleration. Ergot produces these effects mainly through its tyramine, which acts by exciting the sympathetic nerve-endings like adrenalin, and this effect will be increased by the ergamine acting on cardiac muscle. Tincture of ergot contains ergotoxine also, and this will act upon the heart through the sympathetic system and further enhance the action of tyramine.

These effects result in a rise of *blood-pressure*. When crude ergot is directly injected into the circulation an initial fall of pressure is commonly observed. This is due probably to histamine and to such impurities as choline, but this fall of pressure is not seen if the drug is injected subcutaneously. The pulmonary pressure rises at the same time as the systemic pressure on account of the increased output from the right side of the heart, and this is of some importance, as ergot has been administered in cases of hæmorrhage from the pulmonary vessels. Used for such a purpose, this drug could however only act harmfully. Ergot never tends to constrict the pulmonary vessels ; on the contrary, when it is administered

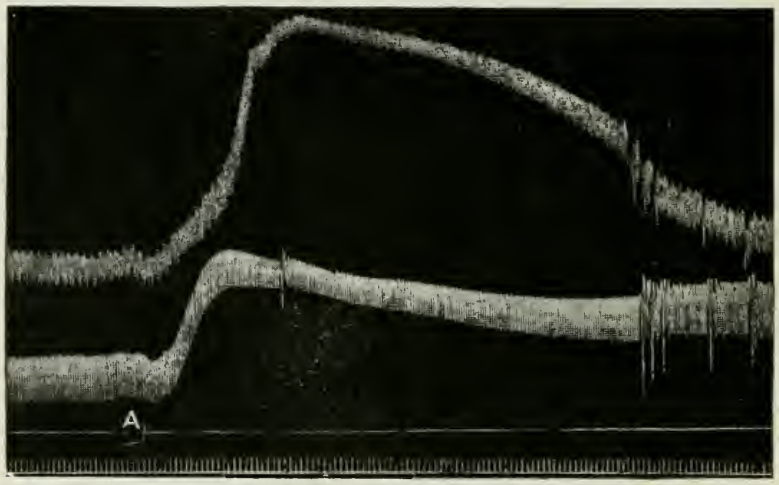


FIG. 64.—DOG (PITHED). ACTION OF ERGOT ON THE PULMONARY VESSELS.

Upper curve = pulmonary pressure, taken with a saline manometer. Lower curve = carotid pressure, taken with a mercury manometer. At A 6 c.c. of liquid extract of ergot were injected into one jugular vein. The increase of pulmonary pressure is due (i) to augmented output from the right side of the heart, and (ii) to augmented pressure on the left side of the heart. Since the pulmonary vessels do not constrict the condition is necessarily associated with congestion of the lungs. The rise in systemic pressure is largely due to vaso-constriction.

to the intact animal these vessels are passively dilated by the rise of pulmonary blood-pressure, so that the outflow of blood from a small branch of the pulmonary vein is even greater after the administration of ergot than before. Nevertheless, one constituent of ergot tends to constrict the pulmonary vessels (ergamine), though this effect can only be observed in a direct perfusion and is of no practical significance (Fig. 64).

Active ergot produces certain secondary effects, which are so characteristic that they are made use of as a physiological test for the drug. If fowls, swine, and other animals are fed with ergotised rye the action of the fungus is manifested by *gangrene* and sloughing of the peripheral parts, such as the comb and wattles of fowls, ears of hogs, and ears, nose, fingers and toes of man. To determine

whether or not a crude sample of drug is active one method commonly adopted is to feed roosters with the specimen, and note whether gangrene appears on the comb and wattles (Fig. 65). Microscopic sections made from the affected parts show the vessels sometimes filled with corpuscles and sometimes with hyaline thrombi: the walls are thickened, and there is hyaline degeneration of the intima. Ergotoxine is the principle chiefly concerned in gangrene production.

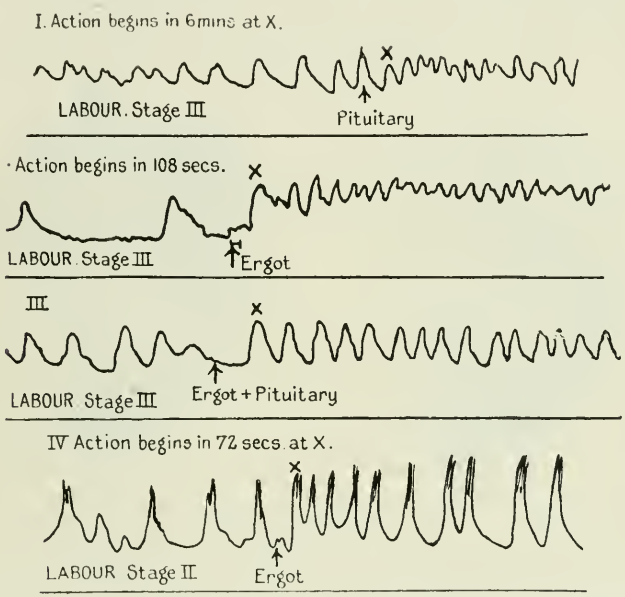


FIG. 64A.—GRAPHIC RECORD OF THE MOVEMENT OF THE UTERUS OF PATIENTS DURING NORMAL LABOUR.

Each record represents about one hour. Upstroke = contraction. The drugs were administered by intra muscular injection at the arrow. The effect begins at the X.
No. I. Begins thirty-five minutes after the birth of the child. Injection 1 c.c. pituitrin which acts in six minutes.
No. II. Begins about four hours after the birth of the child. Injection of ergot which acts in 108 seconds. Note the increase of tone.
No. III. Begins one hour after the birth of the child. Injection of ergot + pituitrin.
No. IV. is taken during the second stage of labour in the expulsion period. Injection of ergot which acts in seventy-two seconds. Each contraction here corresponds with a pain. (Rübsamen.)

Ergot also affects other forms of involuntary muscle, the tonus and peristalsis of the whole gastro-intestinal canal is increased: in therapeutics sufficient amount is not given to make this action of much significance. Ergot is mostly employed on account of its effect on the *uterus*. This action is like that on other plain muscles and shows itself first by the augmented contraction of the fibres as a whole, and by a more active peristalsis. These effects are produced partly through the nervous system by ergotoxine and tyramine drugs, which produce their effect only when the uterus is gravid. But ergot has also a profound effect on the non-gravid uterus, and this is due to ergamine, which acts directly on muscle.

Ergamine increases the tonus and peristaltic waves in the uterus in all conditions, and the effect is far more pronounced than that of any other ingredient of the drug. It is said that after the administration of small therapeutic doses of ergamine the tonus alone is increased and not the movements of the uterus; but it is certain that active ergot in moderately large doses increases both the peristaltic movements and the tonus. This tends to cause augmentation of menstruation—emmenagogue effect—in the non-gravid condition, and abortion—ecbolic effect—in the gravid condition. Ergot is especially valuable in *post-partum* hæmor-

FIG. 65.

Represents the heads of two roosters. A is normal and is given for the sake of comparison. B shows the gangrene of the comb and wattles, after an injection of active ergot.

rhage, chiefly by promoting the contraction of the uterus. These effects are well shown in Fig. 64A in which the movements of the human uterus are recorded graphically during labour. No. 1 shows the effect of pituitary extract for comparison.

Ergot is used occasionally for internal hæmorrhage other than pulmonary.

POISONING

Ergotism is the term applied to the epidemic disease which is caused by eating rye-bread containing ergot. It is now rare, and is epidemic only in certain parts of Russia; in mediæval times, however, epidemics spread over the whole of Europe. They were apt to break out after wet summers and bad harvests, and to cease as soon as the crops of the year had been consumed. The symptoms may be either acute or chronic, but the acute symptoms are extremely rare, and consist of severe vomiting and diarrhœa, with death from collapse—any irritant poison might induce a similar effect. Acute poisoning is probably caused by a large absorption of histamine. The cases of chronic poisoning are very characteristic.

Nervous effects are often the first symptoms to appear during an attack of ergotism. They show themselves especially by disturbances of sensation, which begin at the periphery and spread upwards, parts of the skin being hyperæsthetic and parts anæsthetic at the same time. But the most characteristic sensory affection is that known as formication, which is a sensation as of insects running along the skin ; it is usually present in the limbs alone and is accompanied by severe itching. Sometimes sensation is completely paralysed, and depression or paralysis of the special senses, hearing, sight, and smell, may occur.

Motor affections are also present : twitchings, tremors, severe cramps, and painful spasms are the more common. They affect the extremities, especially the lower, and the extensor and flexor muscles are attacked promiscuously. In some epidemics the motor nervous symptoms are especially pronounced ; in such cases tremors, spasms, involuntary contractions of muscles, or choreic movements are seen, and may lead ultimately to typical epileptiform convulsions, with tonic and clonic spasms, affecting the facial as well as the spinal muscles.

Alimentary effects.—Within a few days of the first ingestion of rye-bread contaminated with ergot, various alimentary symptoms occur, and are associated with the sensory symptoms already mentioned : these are vomiting, diarrhœa, abdominal pains, and, sometimes, tenesmus.

Circulatory effects.—Next to the affection of the central nervous system the circulatory changes are the most characteristic. The pulse is variable ; it is always hard and small, and has all the features of a high blood-pressure. One common type of attack is known as the gangrenous. In this form those affected by the disease suffer intolerable pain, they waste rapidly, the peripheral parts become livid and "icy cold," and gangrene supervenes. These symptoms may come on at any time from two days to three weeks after the other toxic symptoms. Sometimes all the nails, fingers, and toes become at the same time cold, lose sensation, and appear dark and shrunk ; later they fall off. Gangrene of the skin may show itself in the formation of pustules. More rarely, internal organs become gangrenous, and cataract of the eye and ulceration of the stomach and intestines may ensue.

If the uterus be gravid there is a tendency to abort.

From this it is evident that chronic ergotism may be of two kinds, each possessing many characteristics in common, but sufficiently dissimilar to be classed formerly as two distinct diseases.

In the gangrenous type the circulatory symptoms are prevalent, whilst in the convulsant type the nervous symptoms are all-important. In epidemics of ergotism the type of symptoms remain constant, and the difference in the symptoms in various epidemics can only be explained by a difference in composition of the ergot. Different samples of ergot may contain very different amounts

of the three main constituents: with some samples nervous and muscular effects can be induced with ease, whilst with others a considerable rise in blood-pressure and typical gangrene may occur, but little or no apparent nervous effect.

Ecbolics and Emmenagogues

Ecbolics are drugs which are employed to stimulate the gravid uterus to expel the fœtus. When the uterus is not gravid the same drugs increase the menstrual flow, and are then termed emmenagogues. Emmenagogues are sometimes divided into two groups : the direct, which act on the uterus in the same way as the ecbolics, and the indirect, which act either by altering the vascular conditions of the abdominal organs, such as purgatives, or which improve the condition of the blood or the general tonus of the body, such as iron and strychnine respectively.

Ecbolics may be divided into the following groups :—

(1) Those acting on Uterine Muscle :—
- (*a*) *Through the Centre.* Strychnine ; Picrotoxin.
- (*b*) *Through the Ganglia.* Hydrastis ; Conine.
- (*c*) *Through the "Nerve-endings."* Tyramine ; Pilocarpine ; Physostigmine ; Digitalis.
- (*d*) *Through the Muscle-fibre.* Histamine; Veratrine; Quinine; Barium; Lead; Pituitary.

(2) Those producing Congestion of the Pelvic Viscera :—
- (*a*) Drastic purgatives and aloes.
- (*b*) Irritating volatile oils:—savin, thyme, turpentine, penny-royal.
- (*c*) Violent irritants:—cantharidin.
- (*d*) Heat or counter-irritation to pelvic regions:—hip-baths, mustard-plasters, and hot injections into the vagina.

MATERIA MEDICA

Ergota. **Dose, 15 to 60 grs.** (1 to 4 grms.).

Preparations

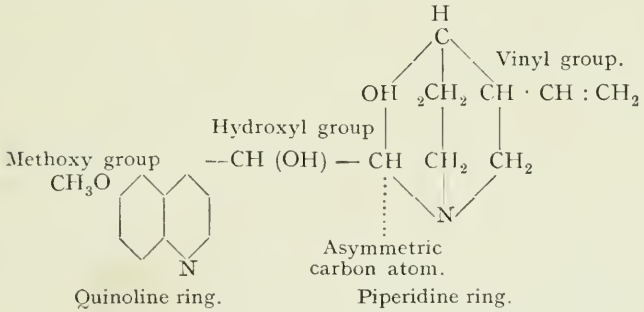
1. Extractum Ergotæ.—Ergotin. **Dose, 2 to 8 grs.** (12 to 50 ctgrms.).
2. Injectio Ergotæ Hypodermica.—33 per cent. of the extract. **Dose, 3 to 10 m.** hypodermically (3 to 6 decimils).
3. Extractum Ergotæ Liquidum. **Dose, 10 to 30 m.** (6 to 18 decimils).
4. Infusum Ergotæ. **Dose, 1 to 2 oz.** (30 to 60 mils).
5. Tinctura Ergotæ Ammoniata. **Dose, ½ to 1 dr.** (2 to 4 mils).

CHAPTER XV

CINCHONA

Red cinchona bark is obtained from the stem and branches of the cultivated *Cinchona succirubra*. The tree is native to South America, but is cultivated in the Dutch East Indies and Ceylon. The chief constituents of the bark are quinine (about 1.5 per cent.), cinchonidine (2.5 per cent.), cinchonine (1 per cent.), and some quinidine, hydroquinine, hydrocinchonidine, and other allied bodies, making up a total of about 5.8 per cent. alkaloid. The bark also contains a glucoside, quinic acid, and a peculiar tannin which yields cinchona red on oxidation.

Quinine has a complicated formula, consisting of a quinoline group attached to a piperidic nucleus. It is isomeric with quinidine ; and cinchonine is isomeric with cinchonidine.



Constitutional Formula of Quinine.

Quinine derivatives are formed by alterations in the methoxy, the hydroxyl, or the vinyl group. The asymmetric carbon atom allows of isomeric modifications.

Cinchonine differs from quinine only in the absence of the methoxy group (O CH_3). If this methoxy group is replaced by the OH radicle we get cupreine. Many derivatives have been prepared by replacing the H of the OH group with another group, so as to form an insoluble quinine ether; these ethers are split up by the alkali of the duodenum into quinine compounds, and are exactly analogous in their relation to quinine as aspirin is to salicylic acid. Such quinine derivations are aristoquinine (diquinine-ester of carbonic

acid), euquinine (ethyl carbonate), and many others. Their insolubility makes them tasteless, but they have no other advantage over quinine. Hydroquinine, from which most of the newer and more valuable derivatives are formed, has the vinyl group $CH=CH_2$ converted into CH_2-CH_3. Ethyl hydrocupreine is hydroquinine in which the methoxy group OCH_3 is changed to ethoxy $O.C_2H_5$, and by substituting the higher homologues we can obtain the iso-propyl, iso-amyl, and iso-octyl hydrocupreines.

Action

External.—Quinine is a general protoplasmic poison, and in sufficient concentration paralyses all forms of living matter. Applied to mucous membranes, solutions of quinine and urea hydrochloride exert an anæsthetic action resembling that of cocaine. The anæsthesia is produced in about ten minutes on the average, and is stated to be very lasting sometimes extending over seven days. It differs from most other alkaloids in that it has no specific affinity for this or that tissue, but behaves alike towards all. It first increases slightly the activity of the tissue, but this very rapidly gives place to paralysis. It is especially fatal to undifferentiated protoplasm and to lower organisms. In the presence of such a dilute solution as 1 in 20,000, vigorous paramœcia after a few minutes become sluggish in their movements, and in two or three hours are completely disintegrated. Fresh-water amœbæ rapidly become spheroidal and motionless in even more dilute solutions such as 1 in 50,000, and should the percentage of quinine be increased they also disintegrate. Movements of cilia and spermatozoa are likewise brought to a standstill. This is particularly easy to observe in the case of cilia. If the pharynx of a frog is pinned out on a smooth surface, a hemp seed will be moved over the cilia by their vibratile activity, and its velocity can be readily determined. After painting the membrane for a few minutes with a dilute solution of quinine the hemp seed is carried along at first more rapidly; but this effect soon passes off, and the movement becomes slower and slower and ultimately ceases. This destructive power in very dilute solution is peculiar to quinine; other bitter substances do not possess it; and although some other alkaloids, such as strychnine and veratrine, have a like action, it is only in much larger doses, and is quite insignificant in proportion to their other effects.

Certain lowly forms of life exist which are able to live in a 1 in 500 solution of the alkaloid; among these are the amœbæ of salt water and the spirochætæ of relapsing fever. Yet we can appreciate no difference in structure between the amœba of our ponds and that of the sea. Again, the spirochæta of ordinary vegetable decomposition and that found in the mouth cannot be distinguished under the microscope from that seen in the blood during an attack

of relapsing fever, and yet quinine in solutions containing 1 part in 10,000 parts of water destroys the former but does not affect the latter: it destroys also the spirochæta of syphilis.

Quinine is antiseptic; in solutions of 0.2 per cent. it prevents the acetic and butyric acid fermentations, and inhibits the growth of yeast and decomposition in organic matter. The drug also retards the action of many unorganised ferments: the activity of pepsin and trypsin is decidedly reduced, and that of ptyalin and diastase in a less degree. If an animal is dosed with quinine and then killed, the *post-mortem* transformation of glycogen into sugar is retarded.

Some of the quinine derivatives exert specific actions in a remarkable degree towards micro-organisms. It sometimes happens that a small change in the vinyl side-chain of the quinine molecule produces a profound difference in its effect on certain bacteria. The reason for this is unknown; it may be due to a very delicate chemical reaction or to some change in physical property which enables the alkaloid to penetrate the bacterium more easily. Below is a table showing the relative bactericidal action of the quinine derivatives on some micro-organisms.

Relative Bactericidal Action of Quinine Derivatives.

	Diphtheria Bacillus.	*Tetanus Bacillus.*	*Streptococcus.*	*Staphylococcus.*	*Pneumococcus.*
Quinine hydrochloride	1:100	1:1,000	1:1,000	1:500	1:2,000
Ethyl hydrocupreine hydrochloride	1:400	1:2,500	—	1:500	1:400,000
Isopropylhydrocupreine hydrochloride	1:800	—	1:8,000	1:1,000	1:200,000
Isoamylhydrocupreine hydrochloride	1:2,000	1:20,000	1:40,000	1:8,000	1:20,000
Heptylhydrocupreine bihydrochloride	1:8,000	—	—	1:64,000	—
Iso-octylhydrocupreine	1:8,000	1:60,000	1:80,000	1:16,000	—
Eucuprinotoxine	—	—	1:60,000	1:52,000	—

Quinine is said to inhibit the oxidising power of protoplasm: it is supposed that this is demonstrated by adding to the watery extract of some living tissue, such as fresh lettuce leaves or potato peelings, a little freshly prepared tincture of guaiacum and ozonic ether; the blue colour which, under ordinary circumstances, at once appears indicates oxidation; if a little of the alkaloid is present in the solution this coloration is very long delayed or absent. Such oxidation is not due to any inherent properties of living protoplasm, but to an unorganised ferment—an oxydase. As further examples of this inhibitory action on fermentation, we

may point to the formation of acid which occurs in drawn blood which Binz believes to be due to oxidation: quinine administered during life retards this *post-mortem* effect. Lastly, it has been shown that when either benzoic acid and glycocoll or salicylic acid and glycocoll are perfused through the isolated kidney, either hippuric acid or salicyluric acid respectively is formed. The presence of 0.5 per cent. quinine diminishes this synthesis to one-sixth.

Two hypotheses have been proposed to account for this action of quinine. The first supposes a direct chemical combination between the alkaloid and albumen, and in favour of this view is the fact that a mixture of albumen and quinine coagulates at a lower temperature than albumen alone, and the precipitate so formed cannot be washed free from quinine. This view, however, does not explain the disintegration of paramœcium. Binz suggested the other hypothesis—that quinine in some way interferes with oxidation. He argues from the fact that the changes produced in the lower organisms are similar to those which occur as the result of a diminution of oxygen.

Absorption and Action on the Blood.—When quinine is taken by the mouth it acts as a bitter, the gustatory apparatus receives a powerful stimulus, and the appetite is improved: gustatory impulses acting reflexly are the strongest of all stimuli to the peptic glands. On reaching the stomach quinine is dissolved by the hydrochloric acid, but has no direct action upon the flow of gastric juice. Passing into the duodenum, it is absorbed rapidly under ordinary circumstances, although, if an excess of alkali be present in the duodenum, it is precipitated by the bile acids, which form with it insoluble salts; in this way it occasionally remains unabsorbed, and can be detected in the fæces.

After absorption quinine exerts a profound effect upon the white blood-corpuscles: this we should expect when we consider the general relationship of these corpuscles to the unicellular organisms we have already mentioned. If 1 part of quinine is added to 4000 parts of human blood, the amœboid movements of the leucocytes very soon cease and the cells become spheroidal. The same fact can be better observed in the frog: if the mesentery of this animal is exposed on the stage of a microscope, inflammation naturally ensues. The white blood-corpuscles are seen to adhere to the walls of the vessels, migrating freely into the surrounding tissues, and changing into pus-cells: at the same time the blood-current becomes slower (Fig. 66, A). If quinine is now injected subcutaneously, the picture undergoes a change. The leucocytes become round and granular, their movements cease, and they no longer migrate through the vessel-walls. Cells which have already migrated pass further away from the vessel, so that a clear space soon becomes apparent between them and the vessel-wall. Yet the circulation remains undisturbed, and the other conditions are all favourable to the formation of pus (Fig. 66, B). If a dose of

quinine is injected into the frog's lymph-sac before the mesentery is exposed, again no pus is formed and the circulation goes on normally. From these experiments it appears that quinine checks suppuration in frogs; but such large doses of the alkaloid are

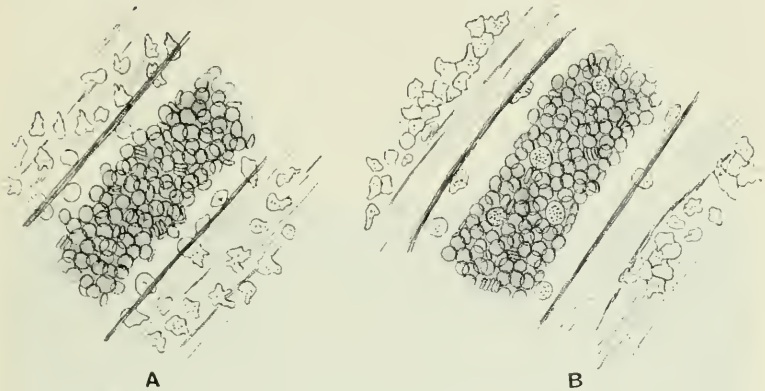


FIG. 66.—MICROSCOPICAL VIEW OF A PIECE OF THE MESENTERY OF A FROG WITH THE CIRCULATION INTACT.

A shows normal suppuration and B is the same view modified by the action of quinine. Note the tendency of the white blood-corpuscles to become round, granular, and immobile; their migration ceases and a clear space forms round the vessel. (Binz.)

requisite to produce any decided effect in mammalia that its employment for this purpose is impossible.

The effect on the leucocytes must not be considered specific, but rather as a type of what is probably going on in all the cells of the body, only as the leucocytes exhibit amœboid movements and are so readily observed, they form a convenient type of cell for study.

Action in Malaria.—Malaria is due to a protozoon which was discovered by Laveran in 1880. Binz, however, from his

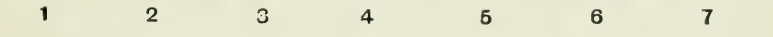


FIG. 67.—PLASMODIUM OF TERTIAN AGUE, SHOWING THE CYCLE OF DEVELOPMENT IN THE RED BLOOD-CORPUSCLE.

Quinine exerts its greatest effect upon the forms which are just breaking up into spores (6) and upon free-swimming organisms (7). It has much less effect on the young endo-corpuscular forms (1, 2, and 3).

experiments with quinine on protozoa, prophesied the discovery of some such organism. The parasite is found in the red blood-corpuscles, where it undergoes certain transformations. There are several varieties of malaria, but the parasite of tertian ague may be taken as a type to indicate the stage during which quinine is

most effective. In its early stages it exists as an amœboid mass of pigmented protoplasm contained within the red blood-corpuscle. Its endo-corpuscular development proceeds for about forty-eight hours, when segmentation occurs, and with it a paroxysm of ague. The segments are arranged as a rosette, and, with the disintegration of the rosette, pigment and young parasites are set free.

If the parasite is examined on the warm stage of the microscope the presence of quinine equal to 1 in 10,000 arrests its movements; but when the drug is given by the mouth three hours elapse before the endo-corpuscular bodies become immobile, granular, and lose their affinities for certain stains. Quinine does not attack the

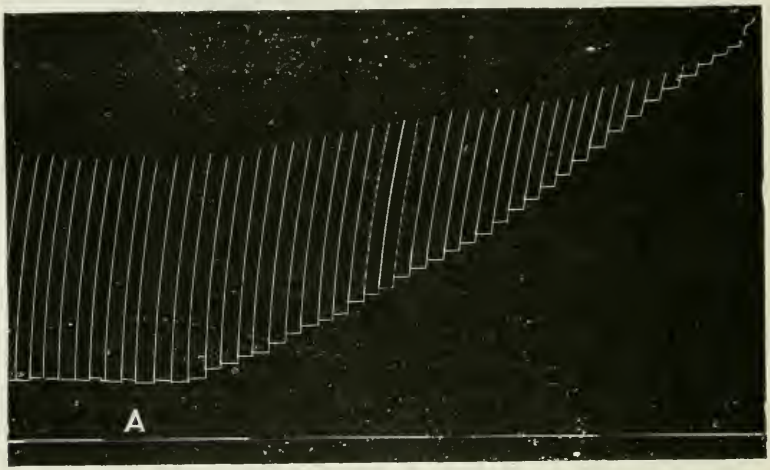


FIG. 68.—ISOLATED GASTROCNEMIUS OF THE FROG, SHOWING THE EFFECT OF A NUMBER OF SINGLE INDUCTION (BREAK) SHOCKS.

At A 1 per cent. solution of quinine was applied directly to the muscle. Death occurs in rigor. Stimulations every ten seconds. After intramuscular injections into man, the quinine is held locally, and is very slowly liberated into the circulation.

parasite with equal virulence in all stages of its development: it is most destructive when it is in the act of breaking up into spores and upon free-swimming organisms; it is least so to the young endo-corpuscular forms. It should be given so that it is present in the blood in the maximal quantity when the spores are being liberated, so that they may be killed and a new cycle of development prevented. If, however, the quinine is given during the intervals of well-being, *i.e.* when the intra-corpuscular forms are present in the blood, it does little good, for it is in this stage that the organisms are most resistant. Quinine should therefore be given a few hours before the paroxysm, so that, by allowing sufficient time for absorption, it may be present in the blood when the spores are being liberated.

Action on Muscle.—Quinine acts to some extent on all forms of muscle: if it is applied to the curarised gastrocnemius of the frog

the contractions are increased just at first, but the irritability is soon diminished and the muscle dies in rigor (Fig. 68). Perhaps the quinine enters into some loose combination because intramuscular injections of quinine in man are useless since absorption is so slow.

On smooth muscle quinine has a somewhat similar effect: when small quantities are applied directly to a stomach-ring preparation from the frog, the automatic movements are increased at first, but with very large doses great relaxation occurs. If the drug is perfused through the vessels of an isolated organ there is initial constriction, soon giving place to dilatation. The intestines, spleen, and uterus are affected in like manner. Quinine may bring on the pains of labour in women predisposed to abortion. But the assertion that it is a valuable ecbolic is disproved by the fact that it is administered indiscriminately to pregnant women without evil effect, although in large doses it contracts the uterus. It is, however, easy to show that injections of quinine increase the uterine peristaltic movements in animals, and the same effect is obtained on the isolated uterus.

The action on the circulatory system is small: in doses of from 10 to 20 grs. the pulse-rate is increased slightly, whilst in larger doses it is diminished, this being probably due to an action on the muscle-protoplasm.

The total effect on muscle is very small and of little practical significance: nevertheless, quinine is said to be a "tonic," a word which is much abused. The term should be limited to drugs which increase tonus, and, so far as muscle tonus is concerned, strychnine is pre-eminently the tonic. The common employment of the term is unscientific, and denotes all remedies which improve the general health and vigour of the patient.

Action on Metabolism.—Quinine diminishes metabolism, but it is a little difficult to understand exactly what takes place. The absorption of food is not affected, so that if a man is in a condition of nitrogenous equilibrium the addition of a little quinine to his food has no effect on the digestive functions, for the amount of nitrogen and fat in the fæces remains constant.

Its influence upon metabolism is shown principally by the changes in the urine; the total quantity of water remains about the same, but all the other constituents are diminished. There is usually a slight increase of the various solids for the first hour or so, but it is altogether insignificant when compared with the subsequent and much more permanent diminution. Not infrequently the total solids excreted within the twenty-four hours after a single dose of quinine may be diminished by 40 per cent. The urea, uric acid, sulphate, phosphate, and chloride, together with the specific gravity, decrease in the same ratio; furthermore, a single dose of quinine administered to an animal in nitrogenous equilibrium causes a fall in nitrogen excretion which lasts for a period of two days. Some drugs diminish the excretion of urea, sulphates, &c.,

but their deficiency in the excretion of nitrogen and sulphur in this form is counterbalanced by a larger excretion of unoxidised substances containing nitrogen and sulphur, such as ammonia, leucin, tyrosin, and crystin. This is not the case after quinine; no such incompletely oxidised substances appear in the urine.

Since proteid metabolism is diminished, it might *a priori* be supposed that the gaseous interchange, *i.e.* the absorption of oxygen and the elimination of carbonic acid, would be correspondingly diminished; such, however, is not the case, for the gaseous exchange is unaffected. This must mean that some nitrogenous food, which under normal conditions would be used up and later appear as solid constituents of urine, is being stored up in the body, and the animal, being in equilibrium, is putting on weight.

Quinine is used in fevers as an antipyretic. When administered in small doses to a normal animal it produces a slight initial rise of temperature, followed by a considerable fall; and if given to an animal with pyrexia a like effect is produced, but the fall in the temperature is much greater.

By the aid of calorimetric experiments it is shown that this fall in the temperature is not associated with an augmented loss of heat; indeed, the opposite is the case, for the loss of heat is less, so that quinine lowers the temperature by diminishing heat-production. In a normal animal heat-formation and heat-loss are balanced by the medulla in such a way that a constant temperature is maintained: after quinine the medulla attempts to diminish the heat-loss in order to maintain the temperature, but the attempt is not successful and the temperature falls. It is proper at this stage to consider the tissue on which quinine acts; it might conceivably be either the centre in the corpus striatum or the peripheral structures, the glands and muscle. It is certainly not on the brain, since the temperature is lowered by quinine even when the cord is cut across Nevertheless, after the administration of quinine the medulla fails to compensate successfully for this subnormal formation of heat, which it should do if the nerve-centres were normal; this suggests that quinine has a small action on the centre. The fall of temperature runs a course parallel to the nitrogenous metabolism as measured by the excretion of nitrogen in the urine.

Gaseous metabolism is not affected by quinine, and yet less heat is formed; therefore, carbonic acid elimination is not a true record of the total heat-formation. It is suggested as a working hypothesis that when proteids undergo oxidation a simpler nitrogenous body and carbonic acid are formed first, and heat is simultaneously evolved. This nitrogenous substance undergoes a further change, perhaps by hydrolysis, in which simple bodies, such as urea, are formed, and with a further output of heat. After administering quinine this latter stage is incomplete, the excretion of urea is diminished, and the body gains in weight, but the carbonic acid output remains unchanged.

Quinism or Cinchonism is the name given to a group of symptoms produced by quinine and chiefly connected with the central nervous system.

Digestion.—Quinine has little effect on digestion, but in large doses it sometimes causes vomiting from its extremely bitter taste and the irritant effect of the salt on the stomach, which, in the absence of a sufficiency of hydrochloric acid, is not easily dissolved. The sulphate is much the most irritant salt; it is soluble in about 800 parts of water. The hydrochloride is not only much more soluble (1 in 36) and less irritant than the sulphate, but it also contains a greater percentage of the base.

Central Nervous System.—Large doses of quinine prove fatal by paralysing first the brain and respiratory centre and later the heart. In animals paralysis of the respiratory centre by such very large doses is easily demonstrated, although at this stage life can be continued by artificial respiration. A little later the heart becomes extremely feeble, blood-pressure falls, and death ensues.

In man fatal cases are hardly ever seen. The symptoms usually observed are giddiness, apathy, headache, mental depression, confusion of thought, a diminished appreciation of pain, and general muscular weakness. In more severe cases these are followed by unconsciousness and collapse, the face becomes pale, the lips blue, respiration slow and shallow, and the pulse slow and almost imperceptible.

In a few cases fever has occurred after quinine without noticeable inflammation of any organ. A blackwater fever, characterised by the sudden appearance of blood in the urine, has been attributed by some to the use of this drug.

Sense-organs.—Some of the most characteristic effects of cinchonism are on the sense-organs. In the case of hearing this is manifested by deafness and humming, hissing, and roaring noises in the ears; they last only a few hours, or at most two or three days. In one case the temperature of the outer ear of a man fell 0.56° C. two hours after taking 17 grains of the hydrochloride, and the external meatus and tympanum were seen to be pale when the action of quinine was at its height. In the cat inflammatory extravasations have been produced in the canalis cochleæ spiralis and other parts of the internal ear by dosing with quinine. Such vascular changes are not constant, and the symptoms are attributed to some change in the nervous mechanism, possibly peripheral, although more probably central. It is only in exceptional instances that quinine produces permanent deafness in man.

Disturbances of vision have been observed frequently after large doses of quinine. The field of vision is contracted and colour vision is especially liable to become confused: sight is impaired and total blindness has been recorded. In these cases the retinal vessels have been found (1) constricted and almost obliterated (2) congested, and (3) unchanged. These vessels behave like other

vessels, and are first constricted and later dilated by the drug. The visual disturbances are due to an action on the nervous system, either on the ganglion-cells in the retina or on the centre in the brain.

Transient affections of the *skin* are especially frequent, and are of vaso-motor origin. They usually occur as an eczema, erythema, or urticaria. Other effects of cinchonism are albuminuria and catarrh of the bladder. We have already noted that a few grains of quinine are said to have caused bloody urine, jaundice, and fever.

Excretion.—About half the quinine absorbed is eliminated mostly unchanged by the kidneys, but a small amount is believed to be converted into dihydroxy-quinine, which is almost inert: traces of the drug are excreted also with the saliva, sweat, tears, and milk. Elimination proceeds somewhat slowly, about forty-eight hours being required for the excretion of a single dose. It seems probable that the other half of the absorbed quinine is destroyed by the tissues.

Action of the other Alkaloids.—Preparations of the bark differ from quinine in being about thirty times more bulky, more astringent, more apt to irritate the stomach and intestines, and more difficult of absorption. The action of the other alkaloids differs from quinine principally in degree: quinine is the best antiseptic, and then follow in sequence quinidine, cinchonidine, and cinchonine: their toxic action, if measured by the effect on striped muscle, takes a different order; here cinchonidine is the most toxic, and then follow quinine, cinchonine, and quinidine.

In animals very large doses of cinchonidine cause convulsions, and the same is true, though to a less extent, of cinchonine. The convulsions are epileptiform, and probably the result of an action on the cerebrum.

Ethyl Hydrocupreine.—There can be no longer any question that this alkaloid kills the pneumococcus in the blood of man when administered in doses that it is perfectly permissible to administer. Results have shown that a bactericidal action for pneumococci is produced in the blood serum of patients if they receive by the mouth an amount of ethyl hydrocupreine hydrochloride corresponding with 0·024 gram per kilogram body-weight per twenty-four hours.

The dose recommended by Morgenroth is 20 to 25 grs. in the twenty-four hours, and this dose is sufficient to render the blood pneumococcidal.

Unfortunately, treatment by ethyl hydrocupreine is not free from danger. It is well known that quinine in medicinal doses may contract the field of vision and even produce blindness. This effect seems to be more pronounced with ethyl hydrocupreine.

MATERIA MEDICA

Cinchonæ Rubræ Cortex.—Red Cinchona Bark.

The Pharmacopœia directs that the bark, used to make the preparations, should contain between 5 and 6 per cent. of alkaloids, of which not less than half should consist of quinine and cinchonidine.

Dose, 3 to 15 grs. (2 to 10 decgrms.).

Preparations

1. **Extractum Cinchonæ Liquidum.**—Standardised to contain a total of 5 per cent. alkaloids.
   Dose, 5 to 15 m. (3 to 10 decimils).
2. **Infusum Cinchonæ Acidum.**—A solution of the sulphates of the alkaloids.
   Dose, ½ to 1 oz. (15 to 30 mils).
3. **Tinctura Cinchonæ.**—Standardised to contain 1 per cent. of total alkaloids.
   Dose, ½ to 1 dr. (2 to 4 mils).
4. **Tinctura Cinchonæ Composita.** Tincture of cinchona; bitter orange peel; serpentary. Standardised to contain 0·5 per cent. of total alkaloids.
   Dose, ½ to 1 dr. (2 to 4 mils).

Quininæ Sulphas. Dose, 1 to 10 grs. (6 to 60 ctgrms.). Soluble to less than 0·2 per cent.

Preparations

1. **Ferri et Quininæ Citras.**
   Dose, 5 to 10 grs. (3 to 6 decgrms.).
2. **Pilula Quininæ Sulphatis.**
   Dose, 2 to 8 grs. (12 to 50 ctgrms.).
3. **Syrupus Ferri Phosphatis cum Quinina et Strychnina.**—Easton's Syrup. Each drachm represents ⅛ gr. of quinine sulphate.
   Dose, ½ to 1 dr. (2 to 4 mils).
4. **Tinctura Quininæ Ammoniata** (quinine sulphate, ammonia, and alcohol).
   Dose, ½ to 1 dr. (2 to 4 mils).

Quininæ Hydrochloridum.—Soluble to about 3 per cent. in water. **Dose, 1 to 10 grs.** (6 to 60 ctgrms.).

Preparations

1. **Tinctura Quininæ.**
   Dose, ½ to 1 dr. (2 to 4 mils).
2. **Vinum Quininæ.**
   Dose, ½ to 1 oz. (15 to 30 mils).

Quininæ Hydrochloridum Acidum. Dose, 1 to 10 grs. (6 to 60 ctgrms.). It is soluble in less than its own weight of water.

Quininæ et Ureæ Hydrochloridum (non-official) is a compound of quinine and urea hydrochlorides. It is soluble 1 in 1 in water. For local applications to mucous membranes 20 per cent. solutions are employed.

CHAPTER XVI

THE COAL-TAR OR AROMATIC GROUP

By the fractional distillation of coal-tar a large number of bodies have been obtained possessing a certain aromatic odour and a constitutional formula containing one or more benzene rings. They all have certain common pharmacological actions:—

(1) Protoplasmic poisons, and therefore antiseptic.

(2) Antipyretic.

(3) Tendency to convert oxyhæmoglobin to methæmoglobin.

(4) Narcotic action on the central nervous system, in large doses followed by convulsions and collapse.

It is necessary to study these actions in further detail.

Pyrexia is probably a protective measure adopted by the organism under special circumstances; in support of this hypothesis two experiments may be mentioned. Rabbits which have been infected with pneumococci live longer in a warm oven than in a temperate room; and animals infected with diphtheria have been found to live longer if their temperature is artificially raised by puncture of the corpus striatum. So that it would not seem to be always advisable to lower the temperature in pyrexia.

I. Antipyretics are drugs employed to lower the temperature in fever. They produce little effect on the normal temperature, but a much greater effect during pyrexia. In health heat-production and heat-loss keep pace with one another; the organism, so to speak, is regulated to a definite temperature by means of a central mechanism probably situated in the corpus striatum. During fever this mechanism is apparently as perfect as in health, but is geared at a higher temperature. These facts may be illustrated by the following experiment. A normal dog, temperature 38.6° C., was placed in the cold till its temperature was reduced to 37.9° C., when it began to shiver—shivering is a protective mechanism and increases the production of heat; it depends on the cerebral hemispheres being intact. The temperature was now raised by external heat to 39.1° C., when the dog perspired profusely: the co-ordination was such that a divergence from the normal of about 0.7° C. elicited a protective increase in the combustion or in the dissipation of heat respectively. The dog was now rendered febrile, its temperature being raised to 40.4° C.; under these circumstances it was found that when the temperature was lowered to 40.2° C. shivering

commenced, and when raised to 40.9° C. there was profuse perspiration. In other words, the regulating mechanism for the new febrile temperature is at least as perfect as it was at the normal temperature. The co-ordination between the two factors which previously kept the temperature at 38.6° C., now keeps it at 40.2° C. If to such a febrile dog an antipyretic drug of the coal-tar series is administered, one which we will assume lowers the temperature to 38° C., a new gear is developed, and the animal reacts so as to keep its temperature at the new level. It appears then that these antipyretics lower the temperature by acting on the regulating centre. This entails an augmented loss of heat, which is brought about mainly by dilatation of the peripheral vessels, and can be measured by calorimetric experiments.

The whole of this antipyretic action would seem to be on the brain. If the corpus striatum is punctured the temperature rises considerably, but it can be reduced by these drugs even when the basal ganglia are severed from the higher centres: if, however, the crura are severed in the posterior part there is still a big rise in the temperature, but it is not influenced by these antipyretics. So that the action would seem to be somewhere in the region of the corpus striatum. Before leaving this point it is important to understand the difference in action between a cold bath and one of these antipyretics. Both produce a fall of temperature as a result of an increased loss of heat from the surface of the body, but the bath does not affect the regulating mechanism, so that increased combustion soon brings the body back to its former temperature: the antipyretic acts more permanently; it attacks the regulating mechanism, which it gears to a lower temperature. If a febrile animal is well wrapped up and kept in a warm incubator so that it cannot lose heat from the surface of the body, antipyrine has little or no effect on the temperature. Many drugs dilate the superficial vessels even more than antipyrine and its allies—for example, the nitrites and alcohol—and after the administration of such drugs the body loses much heat and the temperature falls, but they are not good antipyretics, because the increased loss of heat results in augmented combustion, and so the temperature is kept up nearly at its previous level; in other words, the central gearing is not affected.

There is a second group of drugs which lower the temperature, not by increasing the loss of heat, but by diminishing its production. Quinine is an example of this class, and it decisively diminishes the metabolism; therefore less heat is formed and the temperature falls. Drugs of this class will lower the temperature of febrile animals even when loss of heat from their surface is prevented by keeping them wrapped up in incubators. The fall of temperature after quinine is secondary to the diminished metabolism: the diminution in metabolism commonly seen after the administration of one of the coal-tar antipyretics is the result of the fall of temperature.

II. Methæmoglobin (Fig. 69).—A very large number of widely different drugs convert oxyhæmoglobin into methæmoglobin. It is particularly easy to form this substance by the addition of drugs to drawn blood, when it is readily recognised by its characteristic spectrum. But many drugs which produce this body when added

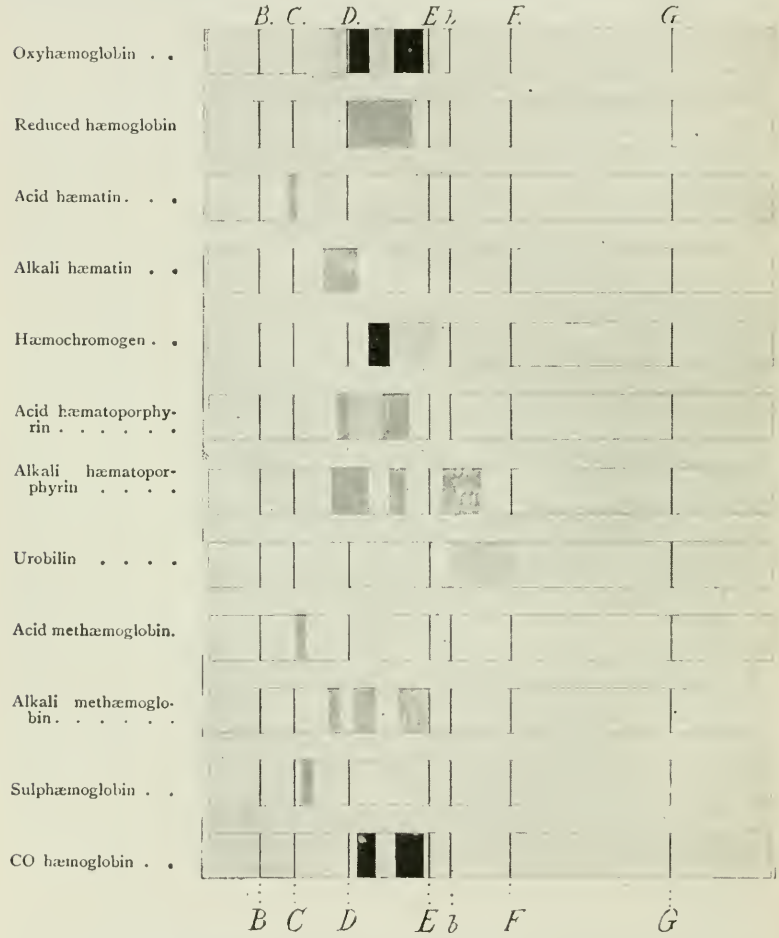


Fig. 69.—Absorption Spectra of Hæmoglobin and its Derivatives.

to drawn blood will not do so when administered to man even in poisonous doses; either death is produced by other means before sufficient drug is in the blood to produce a recognisable amount of methæmoglobin, or the drug is not absorbed, or it is very rapidly excreted. Some drugs, phenacetin and antifebrin for example, form methæmoglobin only when administered to the living animal and not when added to drawn blood.

The presence of a small amount of methæmoglobin gives rise to no evil effects, and after a time it is destroyed and replaced by oxyhæmoglobin. When it is present in larger quantities it causes symptoms which are entirely the result of an absence of oxyhæmoglobin, methæmoglobin being incapable of acting as an oxygen carrier; so the patient becomes blue and dyspnœic. Unless the condition is very severe the methæmoglobin is confined within the red blood-corpuscles; but in some severe cases, as, for example, after a big dose of antifebrin, the methæmoglobin is liberated in the blood (hæmolysis), and remnants of the red blood-corpuscles frequently cause kidney trouble by blocking up the renal tubules at a period when possibly all the methæmoglobin has been replaced by oxyhæmoglobin.

Drugs which produce methæmoglobin may be classified as follows :—

(1) *Oxidising agents : ozone, chlorate of potash, potassium ferrocyanide, hydroxyl and potassium permanganate.*

(2) *Reducing agents : nascent hydrogen, nitrites, all the coal-tar products, but especially pyrogallol and hydroquinone.*

(3) *Indifferent agents, such as salts and glycerine.*

III. Antiseptics and Disinfectants.—Antiseptics are drugs which prevent putrefaction by inhibiting the growth of organisms, whilst disinfectants or germicides are remedies which destroy the germs and their spores. Some antiseptics are also deodorants and are used to hide objectionable smells, such as those arising from putrefaction. A perfect disinfectant should be non-poisonous to man and animals, soluble in water, and rapid in its action; further, it should be non-corrosive to metals and harmless to colours and leather. Very many substances are antiseptic, but only a few are disinfectant, and there is no hard-and-fast line between the two groups. The germicidal power of a solution depends upon its strength, and a substance which will kill growths in one strength will only inhibit them when diluted; thus a 5 per cent. solution of carbolic acid kills anthrax bacilli, but a 1 per cent. solution only inhibits their growth. One body may be disinfectant to one organism but only antiseptic towards another, and some even have a selective action for certain micro-organisms.

Disinfectants may be of two kinds, physical and chemical. Fresh air and sunlight alone will kill many sporeless pathogenic bacteria, and fire, hot air, and steam are all extensively used for disinfectant purposes. Of the chemical disinfectants the most commonly used are included in the following list :—

Perchloride of mercury ($HgCl_2$) is one of the most useful disinfectants with which we are acquainted. It dissolves in sixteen parts of cold water, and a solution of 1 in 1000 kills anthrax, diphtheria, glanders, and typhoid bacilli, and the vibrio of cholera in ten minutes; if the solution is 1 in 400 or 1 in 500 the spores also are destroyed. The disadvantages are that it is very poisonous to

man, corrodes metals, and combines with albumen, forming an albuminate, on which account it is not good for the disinfection of fæces unless acid is also present. For the prevention of these precipitates with albuminous matter the addition of hydrochloric or tartaric acid has been found satisfactory. It is irritating to the tissues.

Mercuric iodide (HgI_2) is more powerful than the chloride, and less poisonous to animals. It has the disadvantage of being insoluble in water unless potassium iodide is present.

Coal-tar Derivatives or Aromatic Series.—The members of this series were introduced by Lister to prevent the infection of wounded surfaces in surgery. Carbolic acid or phenol (C_6H_5OH) is the best known of the group, and is a reliable antiseptic, although not a very powerful germicide. For disinfectant purposes solutions should not be more dilute than 1 in 20, and their activity is considerably increased by the addition of a neutral salt. Blood containing anthrax bacilli can be sterilised by a 1 per cent. solution in about a minute, but the spores require to be soaked for two days in a 5 per cent. solution before they are destroyed. The disadvantages of carbolic acid are that it is poisonous, it coagulates albumen, and has a caustic action on the tissues. Most of the aromatic series do not enter into chemical combination with proteins, and have, therefore, better penetrating power than the metals. A great many are in common use, such as cresol, β-naphthol, salol, salicylates, guaiacol, cresols, ichthyol, izal, lysol, and creolin. The latter four are mixtures of various coal-tar derivatives, and are more efficient for general use than carbolic acid, although a 5 per cent. solution is still requisite for a germicidal effect. Chinosol may be taken as one of the most efficient members of the group: it is soluble in water, non-corrosive, and does not coagulate albumen, whilst in germicidal action it is about as powerful as corrosive sublimate.

Acids.—The mineral acids and acetic acid all disinfect when used in sufficient strength. Their germicidal power varies with their electrolytic dissociation, that is, with the concentration of the H ions in the solution; hence they have a specific action depending on the H ion.

Alkalies.—KOH, NaOH, AmOH, and LiOH are antiseptic and disinfectant. They have been shown to act in proportion to the concentration of the (OH) ions in the solution.

Halogens. — Chlorine and bleaching-powder ($CaCl_2.CaCl_2O_2$). Chlorine is obtained from bleaching-powder by the addition of sulphuric acid. It acts by virtue of its affinity for water, hydrochloric acid being formed and nascent oxygen liberated. 0.3 per cent. chlorine kills minor organisms which are freely exposed in air saturated with moisture. For disinfection purposes 0.5 per cent. should be present in the atmosphere, which would entail about 3 lb. of bleaching-powder for every 1000 cubic feet of air-space. The action of bleaching-powder depends upon the chlorine given off in solution. It corrodes metals and dissolves albumen, but is

cheap and manageable. A 10 per cent. solution is very potent, and 1 per cent. suffices for most purposes.

Oxidising Agents.—Ozone, hydrogen peroxide. Terebene and preparations such as sanitas are good deodorants, and produce a trace of ozone. Potassium permanganate ($K_2Mn_2O_8$) is non-poisonous, readily soluble in water, but quickly loses its colour in the presence of organic matter by the abstraction of its oxygen. To destroy bacteria the solution should contain 5 per cent. permanganate after all organic matter has been oxidised. Such a concentration stains most objects and renders its use impracticable.

Reducing Agents.—Formalin is a 40 per cent. solution of formic aldehyde (H.COH) in water. It is cheap, and harmless to colours and metals except iron. A $\frac{1}{2}$ per cent. solution kills most organisms. Sulphites and ferrous salts also act by reduction. Sulphur dioxide (SO_2) is unsatisfactory as a disinfectant; it bleaches vegetable colours, attacks iron, and injures cloth and leather. Ten per cent. of the gas in moist air fails to destroy the spores of anthrax in twenty-four hours. "Formamint" tablets, in which formic aldehyde is combined with milk sugar, the drug being liberated on solution, are used to disinfect the mouth. (*See* p. 424.)

Salts, especially $CuSO_4$, $ZnCl_2$, Fe_2Cl_6, and most of the salts of Zn, Cu, Fe, As, Pb, Hg, are germicides. Broth, gelatine, or similar organic media diminish the disinfecting power of aqueous solutions of metallic salts.

Method of Determining the Antiseptic and Disinfectant Power of Drugs

The antiseptic dose of a drug may be regarded as the smallest quantity of an antiseptic capable of arresting the development of bacteria in a culture medium. A number of tubes of sterile bouillon are prepared, each containing, say, 10 c.c.; to these is added a varying proportion of the antiseptic under examination. Each tube is inoculated either with the organisms of putrefaction or some other germ, and is placed in the incubator for periodical examination. If the drug is acting as an antiseptic it should inhibit all growth.

To determine the germicidal dose, the drug, in known strength, is placed for a given time in contact with different micro-organisms: this may be done by impregnating test-tubes containing known proportions of the drug in solution either in broth or water, with putrefying micro-organisms and pathogenic bacteria. Water is especially necessary where drugs which act on albumen and the organic media in broth are being employed. After a suitable time culture is made from this into sterile broth, and after incubation for twenty-four hours new cultures are again made into fresh sterile broth, the object of the re-culture being to wash the organisms free from antiseptic. If the last tube is sterile after incubation it shows that all the micro-organisms have been destroyed.

In testing the action of gaseous disinfectants the more resistant

micro-organisms are generally employed, such as anthrax spores. Strips of linen are smeared with the material containing the spores and are exposed to a known percentage of the gas for a definite time, and finally tested by culture or inoculation into animals.

Mode of Action—Antiseptics produce their effects by virtue of their chemical and physico-chemical affinity for various constituents of bacteria. The protoplasm of bacteria does not behave differently from that of other cells as regards permeability to antiseptics: the spores of bacteria, on the other hand, are permeable to antiseptics only with great difficulty. The rapidity with which antiseptics enter the cell is mainly dependent on their solubility in the lipoids forming the limiting layers of the cell, and this solubility closely resembles that in fats. So that the absorption of antiseptics by bacteria depends on the partition coefficient of their solubility in water and in fat-like bodies. Inorganic salts which are not soluble in fats are hardly absorbed until such time as they have destroyed the limiting layer of protoplasm which may enable them to penetrate.

Antiseptics may, therefore, be classified into two groups, according to the manner in which they gain admission to the cell: (1) those which penetrate by virtue of their solubility in fat-like compounds, and (2) those which are insoluble in fat-like compounds but which nevertheless penetrate the cell by first destroying the limiting layer.

But all substances which penetrate the cell are not necessarily valuable antiseptics, otherwise the group of indifferent hypnotics which are very easily soluble in lipoids should form excellent antiseptics; an antiseptic, therefore, must not only be capable of entering a cell, but it must exert also some destructive action on the protoplasm. The difficulty of destroying organisms in the living body by antiseptics can now be appreciated; a substance is required which not only enters the bacterium but which has a selective affinity for its protoplasm and no other.

The efficiency of antiseptics varies not only with their concentration and duration of action but also with the chemical composition of the medium in which they act; in culture media or solutions of proteins their action is much weaker. Two or three times as much perchloride of mercury are required to kill spores in blood-serum as in distilled water.

(1) *Salt Action.*—Common salt, potassium nitrate, and sugar are examples. They act, as a result of their osmotic properties, by extracting water from the organisms and so inhibiting their growth.

(2) *Oxidation.*—Potassium permanganate, hydroxyl, chlorine, and iodine may be taken as examples. All these liberate nascent oxygen, which directly destroys the living matter. The halogens only act in the presence of water, from which they abstract hydrogen to form the haloid acid and liberate nascent oxygen.

(3) *Reduction.*—Typical drugs acting in this fashion are formic aldehyde and sulphur dioxide. The latter requires water as shown by the following equation :—

$$SO_2 + 2H_2O = H_2SO_4 + H_2$$

(4) *Precipitation of Proteins.*—Many of the heavy metals act as antiseptics by precipitating proteins. The effect as regards the bacterium may be slight with dilute solutions, as the metallic albuminate formed round the cell-wall may prevent further action, but they also precipitate the food material and so bring about an antiseptic effect from starvation. On the other hand, by precipitating the limiting layer of the bacterium the metal may obtain entrance to the cell.

(5) *Specific Protoplasmic Poisons.*—The members of the coal-tar series, the essential oils, mercury, boric acid, and borax are typical examples. We have already had occasion to point out that the disinfectant action of salts, acids, and alkalies varies directly with their degree of dissociation. Thus $HgCl_2$, $HgBr_2$, HgC_2N_2 destroy micro-organisms just in proportion to their degree of dissociation, the cyanide and also the oleate being almost useless since they do not ionise in solution. $HgCl_2$ is a better disinfectant than $Hg(NO_3)_2$ or $HgSO_4$, although the two latter salts are dissociated to a greater degree than the chloride. This is an exception to the general rule, and may be explained by the fact that the perchloride is soluble in lipoids to a considerably greater extent than the other salts, and therefore penetrates into the bacteria easier. The action of aqueous solutions of $HgCl_2$ is retarded by the addition of hydrochloric acid or a haloid salt, probably on account of retarded dissociation. In conducting comparative researches on the germicidal action of two substances it is necessary to employ equimolecular quantities. For example, in the case of the acids and alkalies equimolecular solutions are the only ones which are comparable, for these substances act in proportion to the concentration of the H ions and OH ions respectively in the solution.

It is important to bear in mind that the antiseptic action of a drug varies not only with the nature and concentration of the drug, but with the solvent used and the proportion of salts present. Thus, bodies dissolved in methyl-alcohol, ethyl-alcohol, or ether are almost without effect on anthrax spores, whilst the germicidal power of phenol or formalin diminishes as alcohol is added to the solution, since the antiseptic is held fast and does not penetrate.

The choice of a suitable drug is determined largely by the object which is to be disinfected.

For *rooms*, water, soap, and fresh air are the best. Fumigation with sulphur dioxide or chlorine is largely practised, but a spray of formic aldehyde is more efficient than either.

Clothing and bedding are generally disinfected by steam. A

5 per cent. solution of carbolic acid and a 1 in 2000 of mercury perchloride are also employed.

For *excreta*, carbolic acid or some other coal-tar derivative, sulphate of iron, and alkalies are among the drugs more commonly used. If perchloride of mercury is employed some acid must also be added to avoid the combination of the mercury with the albumen.

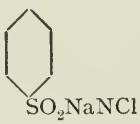
Salts are extensively used to preserve *meats* and meat-extract; and sugars to preserve fruits. Other preservatives are borax, boric acid, and salicylates; but it is an open question whether their employment is harmful to the consumer.

For the *skin*, carbolic acid, about 5 per cent., or ichthyol, up to 50 per cent., may be employed.

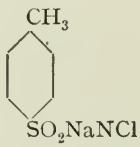
For the treatment of *infected wounds* the hypochlorites, chloramines, and acridine derivatives are principally employed because, besides being powerfully antiseptic, they are believed to be without irritant action, harmless to leucocytes, and non-poisonous.

When a solution of a hypochlorite, or free hypochlorous acid, acts upon organic substances containing the $=NH$ group, the first reaction consists in the replacement of hydrogen by chlorine with the formation of substances of the group known as *chloramines*. Proteins, such as blood-serum, egg white, and casein, treated with hypochlorites, behave thus and give products of high antiseptic value; such compounds are formed in wounds treated with hypochlorites.

Certain aromatic chloramines are stable and form soluble sodium salts. Benzene-sodium-sulphochloramide and paratoluene sodium-sulphochloramide are practically non-irritating, and can be used in much higher concentration than the hypochlorites. Their action is similar to that of hypochlorites, but more powerfully antiseptic.



Benzene sodium sulphochloramide.

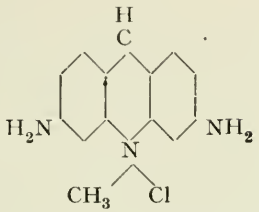


Paratoluene sodium sulphochloramide. (Chloramine T.)

The table on p. 239 shows the relative action of antiseptics on staphylococci.

A number of acridine dyes have an enhanced bactericidal power in the presence of serum, and amongst these the compound, diamino-methyl-acridinium chloride—"flavine"—stands foremost. This substance has been found to be twenty times more powerful than

corrosive sublimate, and 800 times more so than carbolic acid or chloramine under these conditions.



Flavine.—Flavine, then, differs from other antiseptics in that its value is not diminished by admixture with serum and, as it has little local effect on leucocytes and other tissue, it might be an ideal antiseptic. Unfortunately, its use is not free from danger; if much is absorbed, poisoning with œdema occurs.

These drugs cannot be administered internally in sufficient doses to produce a *germicidal effect after absorption*, but it is possible that some beneficial antiseptic effect may accrue. For the lungs, such drugs as guaiacol, creosote, and the essential oils are most general.

Antiseptic.	*Without Blood Serum.*	*With Blood Serum.*
Phenol	1:250 – 1:500 +	1:50 – 1:100 +
Salicylic acid	1:2,500 – 1:5,000 +	1:100 – 1:250 +
Hydrogen peroxide ..	1:3,500 – 1:8,000 +	1:1,700 – 1:2,000 +
Iodine	1:100,000 – 1:1,000,000 +	1:1,000 – 1:2,500 +
Mercuric chloride ..	1:5,000,000 – 1:10,000,000 +	1:25,000 – 1:50,000 +
Silver nitrate	1:1,000,000 – 1:10,000,000 +	1:10,000 – 1:25,000 +
Sodium hypochlorite ..	1:500,000 – 1:1,000,000 +	1:1,500 – 1:2,000 +
Paratoluene sodium sulphochloramide ..	1:750,000 – 1:1,500,000 +	1:2,000 – 1:3,000 +

The figures indicate the concentration of antiseptic necessary to sterilise one drop of a fresh culture of *Staphylococcus aureus* in a total volume of 5 c.cm. acting for two hours. + indicates growth; – indicates complete sterilisation.

These are partly excreted by the lungs, but it is very doubtful if the small amount so excreted can produce much effect, and the sputum is certainly not rendered less virulent when injected into animals.

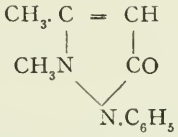
For the alimentary canal, calomel, carbolic acid, β-naphthol, and salol may be taken as typical representatives. We have an indication of the amount of bacterial action going on in the alimentary canal by the amount of ethereal sulphates present in the urine, provided aromatic substances are not being administered. Now, although these drugs do not diminish materially the number of, let us say, typhoid bacilli in the fæces during an attack of typhoid fever, yet by changing the environment of the pathogenic organisms it is probable that their activity is diminished and, therefore, their virulence ; hence, after the administration of a drug such as calomel, there is diminution in the indoxyl and combined sulphates of the urine. Izal is especially valuable as an alimentary disinfectant.

For disinfection of the urine, acid sodium phosphate, hexamine, and the balsams are, perhaps, the most important drugs. Acid sodium phosphate is excreted by the urine, which it renders acid. It is the best drug we possess for increasing the acidity of the urine. Hexamine is excreted partly unchanged and partly as formaldehyde ; it produces a marked effect on putrefactive organisms in the bladder. The balsams and resins are also excreted by the urine and are useful antiseptics.

IV. The ACTION ON THE CENTRAL NERVOUS SYSTEM consists of a mild narcosis shown by a tendency to sleep and a diminished sensibility to pain. The depression begins with the highest centres and works downwards in an evolutionary order. During the recovery increased reflexes and convulsive starts occur, which seem to be comparable with those sometimes seen during recovery from a large dose of morphine. Death, when it occurs, is caused by collapse. The several members of the coal-tar series exert these actions in very different degrees, but it is convenient to divide them into two groups: (1) an **antipyretic group**, whose characteristic action is on the brain and particularly on the heat-regulating centre, and (2) an **antiseptic group**, the members of which are much more powerful protoplasmic poisons.

THE ANTIPYRETIC GROUP

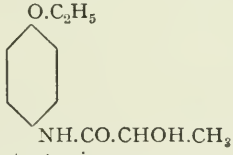
Phenazone or antipyrin is usually obtained by the interaction of phenyl-hydrazine with aceto-acetic ether.



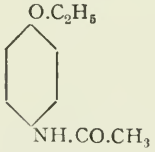
It has a complex structural formula. *Hypnal* is a combination of antipyrine with chloral, and *resopyrin* with resorcin; and other compounds are from time to time put on the market as substitutes for antipyrin.

Phenacetin (para-acet-phenetidin) is prepared from para-nitro-phenol.

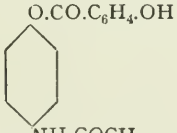
In recent years many allied bodies have been introduced, such as lactophenin, salophen, phenocoll.



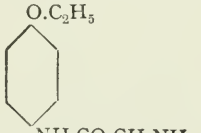
Lactophenin.



Phenacetin



Salophen.



Phenocoll.

Acetanilid or antifebrin is obtained by the interaction of aniline and glacial acetic acid. Allied substitution derivatives, such as

Acetanilid.

Exalgin.

exalgin, have also been employed. The only three which are in the

Pharmacopœia, and which we need consider, are antipyrin, phenacetin, and antifebrin.

Action

These drugs, unlike many other allied bodies of the antiseptic group, are not very poisonous. Their most interesting action is on the body temperature. It is insignificant on the normal temperature, but in fevers, especially those of the intermittent type, where the temperature rises every night and falls to normal or nearly normal in the morning, it exerts its maximum effect, whilst it is less marked in continuous fevers. Any of these drugs will reduce fever with certainty in from one to two hours after administration.

The temperature of the body may be reduced either by increasing the loss or diminishing the production of heat. The coal-tar derivatives lower temperature by increasing the heat loss. This may be shown by calorimetric experiments such as the following:— A rabbit is rendered febrile either by the injection of septic material or by puncture of the corpus striatum, and the amount of heat given off in unit time under fixed conditions is measured. An injection of some antipyretic is now administered and a fall of temperature is obtained, which is accompanied by a corresponding increased loss of heat. This loss might be due to dilatation of peripheral vessels or to augmented perspiration. The latter, although it no doubt assists in the dissipation of heat, is a comparatively unimportant factor, since atropinised animals, with the nerve termination of the sweat-glands paralysed, which therefore cannot sweat, still react in the same way towards these antipyretics. This vasodilatation is seen readily enough in both animals and man: it only affects the skin, and the splanchnic vessels are not simultaneously dilated. This is important, because it shows, in the first place, that the action is not peripheral, for then all the vessels would probably be affected in the same way; further, if it affected all the vessels the blood-pressure would fall and the total blood passing through the skin-vessels would be small, whereas, if the other vessels are unaltered, and only the cutaneous vessels are dilated, then the blood-pressure will not be much affected, and a greatly augmented quantity of blood will pass through the peripheral vessels.

That this dilatation of skin-vessels is due to an effect on the centre is certain, since antipyrin will not lower the temperature after section of the cord. So that we must conclude that the action is on the heat-regulating nervous mechanism.

It was formerly believed that these antipyretics lowered temperature, at least in part, by diminishing the production of heat—the result of a lessened metabolism. A drug which alters metabolism of tissues will act in health as well as in fever—for example, quinine lowers the temperature in fever by diminishing the metabolism of tissues, but it affects metabolism equally well when the temperature

is normal. Now antipyrin, phenacetin, and antifebrin have very little effect on the metabolism of the healthy man; antifebrin is even said to increase it slightly, and in large doses (non-medicinal) it certainly does so to the extent of 20 or 30 per cent. When these drugs are administered to a fevered animal it is true that the metabolism is diminished, but this is due to the fall of temperature, and always comes on after the temperature has commenced to fall. There is no reason for supposing that any of these drugs directly depress metabolism, and no part of their antipyretic action is due to this cause.

It may be noted here that certain other effects occur in the febrile patient as a result of the fall of temperature, and not from a direct action of the drug. The pulse becomes stronger and slower, and the respiration slower and easier.

Action on the Central Nervous System.—The second important action of these drugs is on the nerve-centres, though what the exact nature of this action is we do not understand at present. They produce a slight tendency to sleep and a diminished sensibility to pain; at the same time the reflex excitability of the cord is slightly diminished. They are used with great success in painful conditions such as neuralgia and headache. These hypnotics do not resemble the chloral group since they diminish sensibility to pain, but they rather simulate some of the opium alkaloids; and the likeness is the more complete since with larger doses they tend to produce convulsant effects which in every way resemble those produced by strychnine, the seat of action being mainly the cord. Later, the whole of the central nervous system becomes depressed. Though no longer used to produce antipyresis they are, nevertheless, employed in febrile conditions, though in small doses as narcotics. They relieve objectionable symptoms of fever, such as the pains, headache and restlessness, and promote sleep.

Red Blood-Corpuscles.—If the members of this series are added to drawn blood they produce no effect on the hæmoglobin; this is in contrast with the other representatives of the coal-tar series. When, however, they are administered to the living animal or man they induce the formation of methæmoglobin, at first in the substance of the red cell, but with large doses the methæmoglobin is set free and the cells remain in the circulation as shrunken and colourless *débris*. These antipyretic drugs are oxidised in the body to para-

amido-phenol or an allied substance, and, in proportion as this body is produced, methæmoglobin is formed. Antipyrin differs in structure from the other members of the series, and passes through the body unchanged. Antifebrin, which is readily oxidised, is much more toxic, and produces methæmoglobin much more

readily than phenacetin, which undergoes oxidation more slowly. From this it is easy to understand why methæmoglobin is not produced when the drugs are added to drawn blood.

They all have some **antiseptic** action, although it is not sufficiently marked to make them of much practical value in this respect. Some of the members have been used as dusting powders for wounds.

The action on the **heart and vessels** is of little importance. All the coal-tar series slightly quicken the beat. This is a peripheral effect, probably on the muscular substance of the heart, for it is produced on the excised organ which is being artificially perfused with a saline solution. The vessels are but little altered, although the artificial perfusion of antipyrin through the limbs of a cat slightly augments the flow: it is doubtful whether sufficient drug is ever present in the blood of an intact animal to produce this effect. After the administration of big doses the heart becomes slower.

Idiosyncrasies.—Some people show a remarkable idiosyncrasy to these drugs: if they are administered to such people, even in small quantities, they lead to an alarming train of symptoms. With large doses similar symptoms may be induced in all people. The following are the more important of these:—Disturbances of the alimentary canal, as shown by nausea and vomiting. The face becomes livid from the formation of methæmoglobin, and in very severe cases blood may be detected in the urine. The skin breaks into a profuse perspiration, and erythematous rashes, resembling those of scarlatina or measles, may appear: they are due to alterations in the peripheral circulation. The most serious effects are the attacks of fainting which sometimes occur, and collapse, which has been the cause of death in a few cases. The recorded deaths from collapse have generally been in febrile cases, and are not solely the effect of the drug on the medulla. If one lowers the temperature suddenly, shivering and rigor may follow from an attempt of the centre to increase the heat-production, but a more serious effect may occur; by the removal of the stimulus of fever the partly exhausted nervous and circulatory symptoms may show signs of failure, and so induce the collapse which is characterised by very shallow respiration, an almost imperceptible pulse, and subnormal temperature.

Excretion.—Antipyrin is excreted in the urine combined with sulphuric acid, and is not oxidised in the body; this is in contrast with the other members of the series which are oxidised to para-amidophenol or an allied substance, and this body is excreted in the urine combined with either glycuronic or sulphuric acid. The glycuronic acid reduces Fehling's solution, but the reduction is not due to sugar since the urine will not allow yeast to ferment. These oxidation products in the urine impart to it a smoky tint, although this may also arise from methæmoglobin. After taking antipyrin, ferric chloride colours the urine red; after the administration of the

other members of the series, Fe_2Cl_6 usually gives a brownish tint.

Differences in Action.—The action of antipyrin varies with the dose and ceases as soon as the drug is excreted. The principal objection to its use is that it sometimes, though not so commonly as antifebrin, causes untoward symptoms, especially rashes. Phenacetin is much the safest of the antipyretics, as it possesses only feeble toxic properties. After large doses it may give rise to sweating, but cyanosis or rashes are never observed. It is especially valuable as an analgesic. Lactophenin is another perfectly safe preparation. Antifebrin is less soluble but cheaper than antipyrin. It is probably the most toxic of all these bodies, and is especially liable to produce skin-rashes and collapse.

MATERIA MEDICA

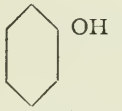
Phenazonum.—Antipyrine. **Dose, 5 to 15 grs.** (3 to 10 dcgrms.).
Acetanilidum. Dose, 2 to 5 grs. (12 to 30 ctgrms.).
Phenacetinum. Dose, 5 to 15 grs. (3 to 10 dcgrms.).

NON-OFFICIAL

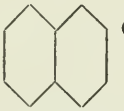
Exalgin.
Dose, ½ to 3 grs.
Salipyrin.—Containing phenazone and salicylic acid.
Dose, 10 to 15 grs.
Lactophenin, *Salophen*, *Phenocoll*, and others.

ANTISEPTIC GROUP

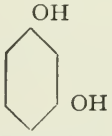
The aromatic bodies included in this group are characterised by a greater toxic action on all forms of living protoplasm than the antipyretic members. The following are some of the more important members in common use :—



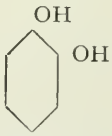
Phenol.



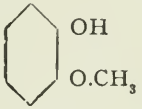
β-Naphthol.



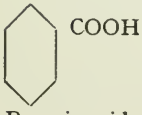
Resorcinol.



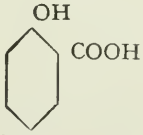
Pyrocatechin.



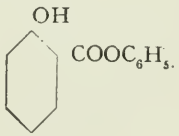
Guaiacol.



Benzoic acid.



Salicylic acid.



Salol.

Carbolic Acid

Phenol (C_6H_5OH), commonly known as carbolic acid, is obtained from coal-tar, and is a typical member of the antiseptic group. When pure it is colourless, and if on exposure to air it becomes brown it shows that impurities are present. It is not an acid, but derives its name from its interaction with strong bases to form carbolates.

$$\underset{\text{Carbolic acid.}}{C_6H_5OH} + NaHO = \underset{\text{Sodium carbolate.}}{C_6H_5ONa} + H_2O.$$

Action on Protoplasm.—Very minute quantities of carbolic acid increase the activity of undifferentiated protoplasm, as may be seen in protozoa, spermatozoa, and cilia. Its effect on bacteria has been especially studied, as it was one of the drugs introduced by Lister as an antiseptic. It has a greater penetrating power than many other members of the coal-tar series on account of its volatility, which enables it the better to exert the specific effect on protoplasm.

A 1 per cent. solution in water destroys the virulence of septic and putrefactive bacteria, and of the tubercle bacillus within a few minutes, but the contact must be continued for many hours to kill the organisms. Spores are extremely resistant, and Koch found that to kill anthrax spores a 5 per cent. solution was required to act for two days.

Carbolic acid precipitates proteins, but it does not enter into chemical combination with them, since it can be washed out from the precipitate, which remains unaltered. In this respect it presents analogies to the precipitation of globulins by alcohol or salts. When it is applied to the skin it produces a sensation of burning, followed by numbness, and the skin looks white and opaque from the precipitation of its proteids. Sometimes use is made of this local anæsthetic action by rubbing carbolic acid on the skin before small operations, such as opening abscesses.

Carbolic acid, taken internally in large doses, causes nausea and vomiting, but in smaller amounts it is used as a gastric antiseptic; it is readily absorbed, and probably circulates in the blood as $C_6H_5.O.SO_2OH$. As it is a general poison to all protoplasm, it produces no very decided specific effects.

Central Nervous System.—The action of carbolic acid on the brain and cord resembles in broad outline that of the antipyretic drugs. It causes a primary slight narcosis, followed in big doses by tremors, spinal convulsions, and collapse, the principal difference from the antipyretic drugs being that collapse is brought about much more readily with carbolic acid. In the early stages of poisoning the respiration and pulse are accelerated, but the respiration soon becomes shallow and irregular and the pulse almost imperceptible—the animal passes into the stage of collapse.

The effects are much the same in man as in animals. The con-

vulsions are particularly well seen in the frog, while the irregular contraction of muscles is more common in mammals; both are of spinal origin. In man convulsions are very rare, probably because collapse ensues before the convulsant stage has time to develop.

Circulation and Respiration.—Carbolic acid, like all the other members of the coal-tar series, accelerates the heart when given in small doses, but with larger doses the heart beats slower: the action is a peripheral one probably on muscle. Respiration is at first accelerated, but the effect is of little importance, and is soon followed by a weak and shallow type associated with medullary depression and collapse.

Carbolic acid does not form methæmoglobin in the living animal.

The **antipyretic** action is due to its effect on the heat-regulating centre, and is brought about by an augmented loss of heat from dilatation of the skin-vessels. After large doses the fall of temperature may be the result of collapse.

Symptoms.—A large dose of carbolic acid, therefore, gives rise to intense pain in the stomach, the result of immediate corrosion, and leads to almost immediate collapse. Supposing that a smaller or more dilute dose has been taken, the local effect is not sufficiently severe to produce collapse, and the carbolic acid will be absorbed. Such a dose will lead to burning in the mouth and throat, nausea and vomiting, followed in a few minutes by stupor, deepening rapidly into insensibility. Convulsions are rare.

Excretion.—Carbolic acid is excreted in the urine mostly as phenyl sulphuric acid,  $O.SO_2OH$. Some is also excreted in combination with glycuronic acid. A very small amount is partially oxidised to pyrocatechin  and hydroquinone  both of which are excreted also in combination with either sulphuric or glycuronic acid. On account of the presence of these bodies, the urine has a smoky tint which, from their further oxidation, darkens on standing. The excretion of the coal-tar derivatives in the urine produces irritation of the kidney, and sometimes leads to acute nephritis, which shows itself by the presence of albumin, casts, and even blood in the urine: irritation, indeed, is so liable to occur that this class of drugs should be administered with caution, especially where there is suspicion of renal trouble.

The urine after carbolic acid will often reduce Fehling's solution owing to the presence of glycuronic acid. The amount of inorganic sulphate is diminished as determined by barium chloride. To

detect the carbolic acid the urine must be made acid and distilled: to the distillate ferric chloride gives a violet colour, bromine water a yellow precipitate from which needle-shaped crystals separate out, and Millon's reagent when heated causes a blood-red coloration.

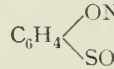
Carbolic acid appears to be normally produced in the body probably as a late product of pancreatic digestion, and Brieger has found that if big doses of tyrosin are taken internally they induce a large increase in the phenol excretion. It is possible that phenol is formed in the intestine by fermentation.

If carbolic acid is injected slowly into the vein of a dog the animal shows all the signs of collapse, the respiration becomes extremely shallow, and the blood-pressure drops. If now a solution of sodium sulphate or, better, persulphate is injected the animal is relieved, respiration recovers, and the pressure rises, but recovery is very slow. The carbolic acid uses up all the available sulphate, and by so doing renders itself comparatively harmless: when further acid is administered severe symptoms at once come on, which in acute cases are not relieved by more sulphate. If a man or animal is suffering from the poisoning of carbolic acid the condition may be gauged by examining the urine. In severe cases all the sulphates will be used up, and although the urine will contain a great excess of aromatic sulphates, yet barium chloride gives no precipitate, showing that the inorganic sulphate is absent. Such a condition is serious, and at once necessitates the injection of sodium sulphate either subcutaneously or intravenously.

Carbolic acid is of historical importance, since it was used by Lister in his antiseptic treatment of wounds, a treatment which was the first step in the development of modern surgery. It is now used mainly to disinfect instruments, excreta, drains, etc. It should be remembered that it is an antiseptic and incidentally a caustic and irritant on account of the ease with which it penetrates tissue colloids. If it is dissolved in a fatty oil it is useless: anthrax bacilli survive immersion in a 5 per cent. solution of carbolic acid in oil for three months; its affinity for oil is greater than that for the tissues. On the other hand, salts facilitate its passage into the tissues by rendering it less soluble in water.

Sulphocarbolates

Sodium sulphocarbolate is the sodium salt of phenol para-sulphonic acid, obtained by the action of sulphuric acid on phenol. It is soluble in five parts of water. It has very little action.



Sodium sulphocarbolate.

Zinc sulphocarbolate.

Zinc sulphocarbolate is obtained by saturating phenol para-sulphonic acid with zinc oxide. It is very soluble both in water and alcohol. Both these carbolates act like carbolic acid, but are considerably less poisonous. The sodium salt is used to disinfect the alimentary canal, but is useless and is excreted unchanged. Zinc sulphocarbolate is used where an astringent as well as an antiseptic action is required.

MATERIA MEDICA

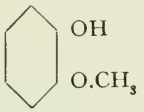
Acidum Carbolicum. **Dose, 1 to 3 grs.** (6 to 20 ctgrms.) in a pill.

PREPARATIONS

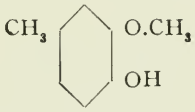
1. **Acidum Carbolicum Liquefactum.**
   Dose, 1 to 3 m. (6 to 18 centimils).
2. **Glycerinum Acidi Carbolici.**—20 per cent.
3. **Suppositoria Acidi Carbolici.**—1 gr. in each.
4. **Trochiscus Acidi Carbolici.**—$\frac{1}{2}$ gr. in each.
5. **Unguentum Acidi Carbolici.**—3 per cent.

CREOSOTE

Creosote is obtained from wood-tar, and consists of a mixture of guaiacol, creosol, and small quantities of other phenols, such as cresol.



Guaiacol.



Creosol.

It has roughly the same action as carbolic acid, but is less irritant and poisonous, and is not so liable to induce collapse. Its absorption and elimination are very rapid; in the urine it occurs mainly as the sulphates of guaiacol and creosol, but a small portion is partly oxidised. Creosote is employed as an antiseptic, in which respect it surpasses carbolic acid. As small quantities are excreted by the breath, it has been employed in purulent bronchitis, and is said to inhibit the growth of pus-forming organisms. It is used also in the treatment of phthisis, and is then best inhaled from a respirator, but it is unable to influence the growth of the tubercle bacillus.

MATERIA MEDICA

Creosotum. **Dose, 1 to 5 m.** (6 to 30 centimils).

PREPARATION

Unguentum Creosoti.—10 per cent.

GUAIACOL

Guaiacol 

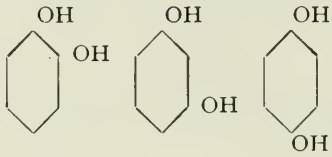
is a syrupy liquid, and forms 60 to 90 per cent. of creosote. It has much the same action as creosote; nevertheless, as a germicide it is inferior to creosote. It is apt to irritate the gastric mucous membrane, and in large doses it depresses the basal ganglia of the brain and may, like acetanilide, cause collapse. Guaiacol carbonate is a non-irritating form in which to administer

the drug in phthisis and typhoid. It is excreted in the urine as an ethereal sulphate.

MATERIA MEDICA

Guaiacol. Dose, 1 to 5 m. (6 to 30 centimils).
Guaiacol Carbonas. Dose, 5 to 15 grs. (3 to 10 dcgrms.).

Resorcin. Pyrocatechin. Hydroquinone (Not official)

These resemble one another closely in their physiological effects, but resorcin only is used to any extent in medicine: it can be prepared from  benzene as a white

Pyrocatechin. Resorcin. Hydroquinone.

crystalline powder. Resorcin was formerly much used as an antiseptic, but now it is superseded by other coal-tar derivatives, which are less poisonous and more active: 1 part in 100 prevents putrefaction of all kinds. Given internally its action is the same as that of carbolic acid: it is but little employed at the present time on account of the ease with which collapse is produced.

The three dihydroxy benzenes have the same pharmacological action, which differs in degree. The meta-derivative is by far the weakest and the para- the most powerful.

Resorcin was formerly used as an antipyretic.

MATERIA MEDICA

Resorcinum. Dose, 1 to 5 grs. (6 to 30 ctgrms.).

Pyrogallol (Not official)

Pyrogallol  occurs as light colourless crystals. When it is injected into animals it produces nervous symptoms like those of carbolic acid. It has a very marked effect on the blood; methæmoglobin is formed, gets into the plasma, and leaves the red blood-corpuscles as shrunken and angular *débris*. Jaundice ensues, and hæmoglobin and methæmoglobin are excreted in the urine. Acute nephritis generally follows, and is recognised by the albumin, epithelium, and casts in the urine. Part at least of the drug is excreted in combination with sulphuric acid and part is oxidised, giving a dark colour to the urine. On account of these symptoms

it is not used internally, but is still employed externally as a parasiticide, the beneficial effects, no doubt, being due to its antiseptic and mildly irritant properties. It is very irritant and stains the skin black.

Ichthyol (Not official)

Ichthyol is a tarry viscid liquid, an ammonium sulphonate of an oil obtained by the distillation of a bituminous mineral found in the Tyrol. It contains 10 per cent. of sulphur. When applied to the skin it produces mild irritation, and is used in ointments as a stimulant. When taken by the mouth its value is doubtful, but it is not very toxic. **Dose, 10 to 30 grs.**

Picric Acid

Picric acid, or trinitro-phenol, has a deep yellow colour in aqueous solution and readily stains nitrogenous fibres such as silk or wool. It is highly explosive (lyddite) and is almost as powerful an acid as hydrochloric. Picric acid combines with proteins and forms a yellow precipitate, and is therefore used as an astringent, a 1 per cent. solution being a favourite remedy for superficial burns and scalds. It is used occasionally for eczema, chilblains, and erysipelas. Taken internally picric acid produces gastro-intestinal irritation with vomiting and diarrhœa. After absorption the skin and urine assume a bright yellow colour and nephritis may occur.

A solution is used to paint on the skin as a disinfectant before operations.

MATERIA MEDICA

Acidum Picricum.

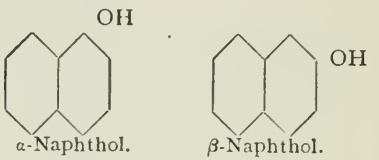
Anilin Dyes (Not official)

Several of the dyes derived from anilin have been employed in medicine. They all possess some antiseptic action, but this is not of a very marked character, being less effective than carbolic acid. Methylene blue is given in doses of 1 to 4 grs. : it colours the urine and fæces a brilliant blue. Injected into living animals it colours nerve tissues blue, especially the axis cylinders. It was considered that this selective action of the dye for nerve might make it of value for the relief of pain, a surmise which has not been realised.

Scarlet red is another dye which causes cancerous proliferation of the epithelium in rabbits. It is sometimes used as a 5 per cent. ointment to stimulate skin growth after burns and other injuries.

Naphthol

Beta naphthol is a by-product obtained in the manufacture of coal-gas. It occurs as a white powder, soluble in alcohol but very slightly soluble in water.



α-Naphthol. β-Naphthol.

It was introduced as a germicide, which might be freely taken internally on account of its slight toxicity. In large quantities the naphthols produce symptoms resembling those of carbolic acid, and during excretion give rise to irritation and inflammation of the kidneys, resulting in the presence of albumin, casts, and hæmoglobin in the urine. β-naphthol is much more active as a germicide than carbolic acid. It is principally excreted with glycuronic acid, but a small amount is oxidised giving the urine a reddish tint. It is used as an intestinal and cutaneous antiseptic. α-naphthol is stated to be more poisonous than its isomer.

Naphthol Salicylate (betol) passes through the stomach unchanged, but is hydrolysed in the duodenum into naphthol and salicylic acid. For use as an intestinal antiseptic the irritant action on the stomach is thus avoided.

MATERIA MEDICA

Naphthol (β-naphthol). **Dose, 3 to 10 grs.**
Naphthol Salicylas (acting like salol). **Dose, 5 to 10 grs.**

Other Coal-tar Derivatives

Cresols. — $C_6H_4\begin{matrix}OH\\CH_3\end{matrix}$. Three isomers occur in creosote. They are excellent germicides, and less toxic than phenol. They are, however, insoluble in water, but are brought into solution by soap as in *Creolin* (from which *Jeyes'* disinfectant is made) and *Lysol*. *Izal* is a milky liquid of similar composition. *Cyllin*, an improved creolin, has sixteen times the germicidal power of phenol on the typhoid bacillus. Some of these, on account of their irritant properties, are unsuitable for internal administration, but some of the less irritant, like izal, have been used as substitutes for the more expensive creosote and guaiacol, and are said to produce the best results in active pulmonary tuberculosis with abundant fœtid expectoration. They are not absorbed easily from the alimentary canal, and are therefore less poisonous than phenol, though they exert the same type of action.

MATERIA MEDICA

Cresol. Dose, 1 to 3 m. (6 to 18 centimils).
Liquor Creosolis Saponatus (50 per cent.).—Made from cresol, castor oil, and potassium hydroxide.

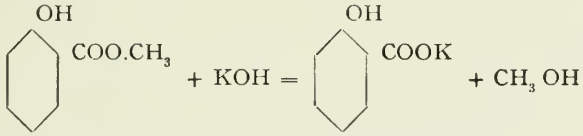
Naphthalin, $C_{10}H_8$, is used to prevent the ravages of moths. In doses of 3 to 6 grs. it is antiseptic and anthelmintic. A very little is absorbed and excreted in the urine as naphthol.

SALICIN. SALICYLATES. SALOL

Salicin is a crystalline glucoside obtained from willows and poplars. On hydrolysis it splits up into glucose and salicylic alcohol or saligenin.

Salicin. $C_6H_{11}O_5.O.C_6H_4.CH_2OH$ + Water. $OH|H$ = $C_6H_{12}O_6$ Glucose. +  CH_2OH Saligenin.

Salicylic acid forms colourless crystals, soluble in 500 parts of cold and 15 parts of hot water. There are two varieties, the "natural" and the "artificial." The former variety is derived from several naturally occurring essential oils which contain the methyl ester of salicylic acid: the oils of winter-green and sweet birch are the two which serve as the chief commercial sources of natural salicylic acid, and they consist of about 99 per cent. methyl salicylate. Salicylic acid is obtained from these by saponification.



Oil of winter-green. Potassium salicylate.

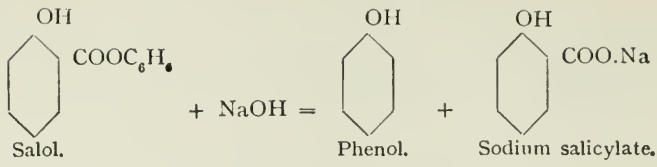
Synthetic or artificial salicylic acid is prepared by the interaction of sodium carbolate and carbon dioxide.

Pure artificial salicylic acid is identical with the natural variety. Formerly the artificial acid was apt to contain impurities, especially

para-oxybenzoic acid,  and the cresols $C_6H_4\langle^{OH}_{CH_3}$, which pro-

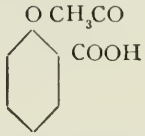
duced unpleasant effects; but it can now be obtained practically pure, and the natural variety, on account of its greater expense, is rarely employed.

Salol results from the combination of phenol with salicylic acid. It is nearly insoluble in water, but is soluble in ten parts of alcohol. Salol is saponified by alkalies.



Such a change is brought about in the living body in the duodenum.

Acetyl Salicylic Acid



Here the acetyl group replaces the phenolic hydrogen.

Action

Salicylic acid has the same type of action as carbolic acid, but it is much less poisonous and less irritant to mucous surfaces. It is a valuable antiseptic, but not being volatile, it has less penetrating power than carbolic acid. In surgery it is useful, and is less irritating to wounds than phenol: 0.15 per cent. prevents the development of bacteria in most organic mixtures, and 0.4 per cent. kills them. On account of their slight taste and freedom from odour the salicylates are sometimes added to beer, wine, and milk to prevent putrefaction. Salicylic acid prevents or hinders the action of enzymes; thus 1 per cent. is sufficient to check the action of ptyalin on starch, whilst to produce this effect with carbolic acid a 10 per cent. solution is required. On undifferentiated protoplasm the action is like that of quinine; the movements of plant protoplasm, of protozoa, leucocytes, and cilia are checked. Salicylates behave like the acid, but they are not quite so effective.

If concentrated salicylic acid is applied to the skin, the horny cells are softened and in time become loosened and separated from the corium without any inflammatory changes being produced: the acid is therefore used to remove thickened epidermis such as one finds in warts.

Alimentary Canal.—When taken internally the acid and salts have the same action. They are much less irritant to the stomach than phenol, and are sometimes employed as antiseptics where there is gastric fermentation. The salicylates are reputed to be cholagogues, increasing both the secretion and salts of the bile. This is, of course, a specific effect after absorption, but it is doubtful if they have such an action, and in any case it is slight and not comparable with the cholagogue effect produced by bile salts.

Salicylic acid is absorbed very rapidly, and circulates in the blood as salicylate of soda.

Action on Metabolism and Temperature.—The salicylates increase the excretion of urea and uric acid. The elimination of sulphur is also considerably augmented, although the relationship between its excretion and that of nitrogen, which in the normal animal is fixed, is now disturbed. After medicinal doses the nitrogen and sulphur may be increased by about 10 per cent., and the uric acid often shows an increase of 50 per cent. It has been suggested that this is due to a more complete elimination of the waste products from the tissues; but it is certainly the result of increased metabolism, since a single dose produces an effect lasting over several days, too long to be accounted for by a more efficient excretion.

The antipyretic action of the salicylates is pronounced. About fifteen minutes after administration, dilatation of the skin-vessels and profuse perspiration appear, soon followed by a fall of temperature. The reduction is apparently due, as in the case of the other coal-tar products, to the increased loss of heat, and the fall of temperature occurs in spite of the augmented metabolism. Salicylates have the power of cutting short an attack of acute rheumatism: how they exert this "specific" effect is not known, and t is likely we shall remain in the dark until we understand something of the pathology of rheumatism. The time taken by the drug to relieve symptoms of pain and fever is often proportional to the dose. An initial dose of 60 grs., followed by 20 grs. every three hours till the temperature is normal, is a not unusual procedure. It is well to prescribe with it some alkali, since in rheumatic disease a tendency to acid formation exists. If a little salicylate is injected into an acutely inflamed rheumatic joint, the result is marvellous: the patient is able to move his joint and the pain disappears. This points to a specific action, since analgesia is central.

After absorption salicylates remain in the blood a relatively long time, and an especially large amount is found to be localized in the joints and muscles, and particularly is this so if the joints are inflamed. If acute rheumatism is a bacterial disease it is difficult to understand how salicylates can produce much effect since they are so feebly antiseptic, and it has therefore been suggested that salicylic acid, which is much more powerful, may be liberated by the CO_2 tension in the blood. Now the CO_2 tension in normal tissues, which is about 6 per cent., cannot effect this change, but when the joints are inflamed the CO_2 tension rises to 15 per cent. or more locally, an amount which is quite enough to cause the change.

Central Nervous System.—Salicylic acid has much less effect on the brain and cord than most of the other members of the coal-tar series. The symptoms of poisoning indicate that the drug in large doses acts upon the cortex, and the headache, disturbances of vision and hearing are probably due to such an effect. After a medicinal dose there is an initial stimulation of the medulla, quite insignificant in character, which shows itself by slight quickening of the respira-

tion and a small degree of vaso-constriction, the latter tending to augment the arterial pressure. After poisonous doses death occurs from paralysis of the medulla, and it is sometimes preceded by asphyxial convulsions.

Poisoning.—When salicylic acid is administered to man in moderately large doses, symptoms develop closely resembling those of cinchonism. There are a feeling of fullness in the head, hissing or roaring in the ears sometimes leading to deafness, and dimness of vision very rarely increasing to blindness. The affections of the sense-organs are associated with vaso-motor changes; congestion of the tympanum and constriction of the retinal vessels have been described. The skin is warm and covered with sweat; there are often rashes of an erythematous, urticarial, or vesicular nature, also vascular in origin. The vaso-dilatation of the vessels of the skin and tympanum and the slight constriction of other vessels are not an uncommon occurrence with drugs, and are due to a central action. Very large doses of most coal-tar derivatives produce irritation of the kidneys; and after giving big doses of salicylates the urine becomes albuminous and sometimes even contains blood. Extreme dyspnœa and collapse have been observed, but are very uncommon. The mental disturbances pass off as the drug is excreted. In some people, who are said to have an "idiosyncrasy," the mental disturbance and affection of the sense-organs are produced by small doses of the drug.

Excretion.—The salicylates are excreted chiefly in the urine as salicyluric acid, a compound formed by the combination of glycocoll, $CH_2.NH_2.COOH$, with salicylic acid

The synthesis of this substance, as in the case of the analogous body hippuric acid, occurs in the kidney: a little sodium salicylate passes through the kidneys unchanged. The green colour of the urine, which is characteristic after the administration of large doses of salicylic acid, is due to the formation of traces of pyrocatechin

and other partially oxidised substances. Salicyluric acid is non-poisonous and has no action in relieving the symptoms of acute rheumatism.

Salicin, administered by the mouth, is converted into salicylic acid in the stomach and intestines. It is less irritant to the mucous membranes than the salicylates, and its action is feebler. The urine contains not only salicyluric acid and salicylic acid but also a small amount of salicyl alcohol (saligenin) and a considerable amount of salicin. Some salicylic aldehyde, which is much more poisonous, is said to be formed in the body, and for this reason Marmé condemned its use.

Salol has no action on the mouth or stomach; it is decomposed in the intestines to salicylic and carbolic acids. It has been employed in the diagnosis of pyloric obstruction: when this condition obtains there is delay in the salol reaching the small intestine, and hence the time is prolonged before salicylic acid can be detected in the urine. Salol is also employed as an intestinal antiseptic, but the putrefaction in the bowels as measured by the amount of indican in the urine remains unchanged. The formation of the carbolic acid, which is much more toxic than salicylic acid, must not be overlooked, and salol should be administered with caution: during excretion it is apt to produce irritation of the kidneys.

Other compounds of salicylic acid are continually being put on the market, but they possess little advantage over the official remedies. Aspirin is a combination of salicylic and acetic acids; it undergoes decomposition in alkaline fluids of the duodenum with the liberation of salicylic acid. Some may be absorbed unchanged, being decomposed by the ferments of the tissues, and hence it may exert a more powerful salicylate action on certain tissues. Like salol, it is excreted only after decomposition.

Methyl Salicylate (oil of winter-green) rubbed into the skin is absorbed locally. It is an invaluable drug for the local treatment of rheumatoid conditions such as lumbago.

MATERIA MEDICA

Salicinum. **Dose, 5 to 20 grs.** (3 to 12 dcgrms.). Soluble to $3\frac{1}{2}$ per cent. in water.

Acidum Salicylicum. **Dose, 5 to 20 grs.** (3 to 12 dcgrms.). Soluble 1 in 500 in water.

Preparation

Unguentum Acidi Salicylici.—1 in 50.

Sodii Salicylas. **Dose, 10 to 30 grs.** (6 to 20 dcgrms.). Very soluble in water.

Salol. **Dose, 5 to 20 grs.** (3 to 12 dcgrms.).

Acidum Acetylsalicylicum (Aspirin). **Dose, 5 to 15 grs.** (3 to 10 dcgrms.).

Methyl Salicylas. **Dose, 5 to 15 m.** (3 to 10 decimils).

Benzoic and Cinnamic Acids

Benzoic acid ($C_6H_5.COOH$) is obtained from (1) benzoin, (2) toluene, (3) hippuric acid. It occurs as colourless crystals soluble in 400 parts of cold and 17 parts of hot water.

Benzoin is a resin from *Styrax benzoin*. It contains about 20 per cent. each of benzoic acid and cinnamic acid, although some varieties, such as those from Siam, contain as much as 40 per cent. benzoic acid and no cinnamic acid.

Balsam of Peru is the product of *Myroxylin pereiræ*. The chief constituent is cinnamein, present to about 60 per cent., and an aromatic oil which consists chiefly of benzyl benzoate, but also contains benzyl cinnamate.

Balsam of Tolu is obtained from the trunk of *Myroxylon toluifera*. It contains 12 to 15 per cent. of free cinnamic acid and about 8 per cent. of cinnamein.

Cinnamic acid ($C_6H_5 - CH = CH - COOH$) is obtained by the oxidation of oil of cinnamon. It is only slightly soluble in water.

Action

Benzoic acid has an action very similar to that of salicylic acid. It is an even more powerful antiseptic, for the presence of 0.1 per cent. inhibits the growth of bacteria, and the salts are nearly as active as the free acid.

Taken internally benzoic acid is rapidly absorbed; it does not produce the symptoms of cinchonism, for even large doses cause only slight gastric irritation, and there are no sense-organ affections so common after taking salicylates. Like all coal-tar derivatives it induces a small acceleration of the heart, followed after very large doses by some slowing.

Metabolism.—On metabolism the benzoates behave like the salicylates. They increase the nitrogenous elimination from the kidneys by augmenting tissue breakdown. The polymorphonuclear leucocytes are increased, but the significance of this fact is unknown. Benzoic acid is frequently used on the supposition that it makes the urine more acid; but this is not the case. It may, of course, render the urine more acid where there is ammoniacal fermentation in the bladder, but this is an antiseptic action and not due to an increased excretion of acid.

Excretion.—Benzoic acid is eliminated by the kidneys combined with glycocoll as hippuric acid  $CO.NH.CH_2.COOH$.

This change is brought about mainly in the kidneys, for, if glycocoll and benzoic acid are perfused by an artificial circulation through the excised kidney, hippuric acid results. Hippuric acid is certainly not formed to any extent in other organs, as moderate amounts injected into the blood cause severe symptoms which cannot be obtained with benzoic acid. A further proof is seen in the fact that no hippuric acid is found in the body if the renal arteries are tied, whilst occlusion of the ureters in no way interferes with the change. In renal disease benzoic acid is excreted mostly unchanged.

The urine contains less aromatic sulphate and indican, and this is regarded as evidence of diminished putrefaction in the intestines, the result of the antiseptic action of the drug. A small amount of

unchanged benzoic acid and a little glycuronic acid, occasionally sufficient to reduce Fehling's solution, may also be detected in the urine.

Cinnamic acid is a powerful antiseptic, and has a pharmacological action similar to that of benzoic acid. It augments slightly the number of the polymorpho-nuclear white blood-corpuscles in the circulation after subcutaneous injection into rabbits, but when it is given by the mouth to man leucocytes are not affected. It has been much vaunted as a cure for tuberculosis, and after its injection changes are stated to take place round tuberculous foci exactly comparable with those which are observed during spontaneous cure. The sodium salt is soluble, and has been put on the market under the name of *hetol*.

MATERIA MEDICA

Benzoinum.

PREPARATIONS

1. Adeps Benzoatus.—Benzoated lard.
2. Tinctura Benzoini Composita.—Friar's balsam. Benzoin, balsam of tolu, aloes. **Dose,** ½ **to 1 dr.** (2 to 4 mils).

Acidum Benzoicum. Dose, 5 to 15 grs. (3 to 10 dcgrms.). Soluble 1 in 400 in water.

PREPARATIONS

1. Trochiscus Acidi Benzoici.—½ gr. in each.
2. Tinctura Camphoræ Composita. *See* Opium.
3. Tinctura Opii Ammoniata. *See* Opium.

Ammonii Benzoas. Dose, 5 to 15 grs. (3 to 10 dcgrms.). Very soluble in water.

Sodii Benzoas. Dose, 5 to 30 grs. (3 to 20 dcgrms.). Very soluble in water.

CHAPTER XVII

DRUGS ACTING LOCALLY ON THE ALIMENTARY CANAL

PURGATIVES. ASTRINGENTS. BITTERS. CHARCOAL

PURGATIVES

PURGATIVES are drugs used to produce evacuation of the bowels. They act by hastening the normal peristaltic movements and by increasing the fluid contents of the intestines. The more vigorous peristaltic contractions frequently give rise to colicky pains and gurgling.

It will be convenient to describe first the vegetable purgatives. Clinicians have divided them into three groups: drastics, purgatives, and laxatives, the activity being in the order stated, but the groups gradually merge into one another, and there is no sharp line of demarcation; thus, an excessive dose of a laxative produces purgation, whilst a very large dose of a purgative drug will induce a drastic action.

Purgatives as a whole can be classed best according to the following schedule :—

CLASSIFICATION OF PURGATIVES

I.—Mineral

(1) *Salines.*—Sodium sulphate, magnesium sulphate, sodium phosphate, potassium tartrate, acid potassium tartrate, sodium tartrate, potassium citrate, lithium citrate, magnesium oxide, magnesium tartrate.

(2) *Mercury.*—Calomel, metallic mercury.

II.—Vegetable

(1) *Laxatives.*—Tamarinds, cassia, manna.

(2) *Oils.*—Castor (ricinoleic acid), croton oil (resin).

(3) *Anthracene Group :*
Rhubarb (chrysophanic acid and emodin).
Senna (chrysophanic acid and cathartic acid).
Aloes (aloin).
Cascara (emodin and frangulic acid).

(4) *Drastic Group :*
Jalap (jalapin and scammonin).

Scammony (scammonin).
Podophyllum (podophyllotoxin and podophylloresin).
Colocynth (colocynthin).
Euonymus (euonymin).

Vegetable purgatives have been described as acting in two principal ways: (1) by increasing the force and rapidity of the normal peristaltic movements, hurrying the food along, and not allowing sufficient time for the absorption of liquid; and (2) by increasing the secretion of fluid from the intestinal walls.

The origin of the fluid of the diarrhœic stool has been a subject of much discussion. Thiry performed a number of experiments with an intestinal fistula. He separated a piece of small intestine, leaving its blood-supply intact, closed one end, and stitched the

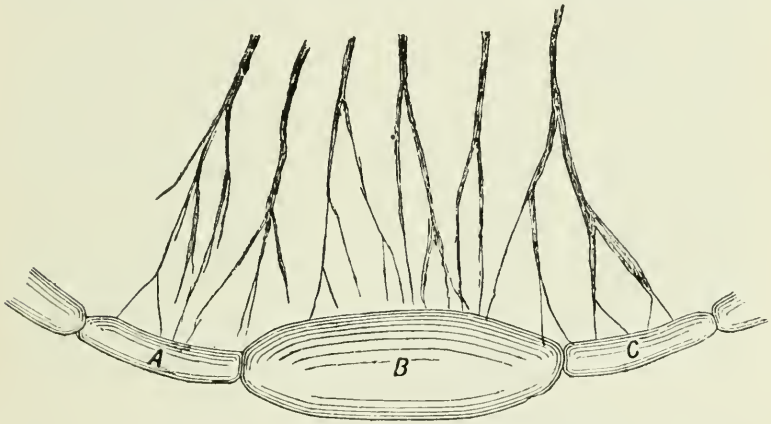


FIG. 70.—DIAGRAM OF MOREAU'S EXPERIMENT.

In this case the intestine of an animal was ligatured so as to form three loops, and leaving the blood-supply intact. *B* received ½ m. croton oil, and *A* and *C*, as controls, each received an injection of water. Three hours later *B* was found filled with fluid which was inflammatory in nature.

other end to the skin. The two severed ends of gut were then fixed together so that the alimentary canal was continuous, and the small isolated portion of it (the Thiry fistula) may be regarded as a sort of test-tube into which we can put drugs and see the effect on the mucous membrane. If a small quantity of a vegetable purgative is placed in this fistula no secretion of fluid follows, although a little secretion is induced by rubbing the mucous membrane with a feather. This would appear to show that secretion from the intestines induced by vegetable purgatives is of no importance.

Moreau devised another method of experiment. He tied four ligatures round the small intestine of an anæsthetised animal, the ligatures being about five inches from one another; three loops of gut were thus enclosed. Into each loop a few drops of fluid are injected by means of a fine needle, that into the central

loop containing the purgative to be tested. The loops are returned to the abdomen, and the animal is kept anæsthetised for about four hours, when it is killed. The central loop *B* is now found to be more or less filled with fluid, whilst the lateral loops *A* and *C*, which serve as controls, are empty (Fig. 70). These experiments have been adduced as evidence that purgatives stimulate the secretion of fluid from the intestines. An examination of this fluid invariably shows that it is inflammatory in nature, that is, it contains a large percentage of protein, and is teeming with granular leucocytes. But the fluid obtained from the filtered diarrhœic stools has none of the characters of an inflammatory exudation; it contains little protein, has a large percentage of common salt, and can digest starch. We have so far, then, failed to produce adequate evidence of the stimulant action of purgatives on the secretory glands of the intestines. What, then, is the origin of the increase of fluid of the fæces after taking a vegetable purgative?

It is completely explained by the increased rate of peristalsis which hurries along the normal secretions from the liver, pancreas, and intestines, giving insufficient time for their absorption; and, moreover, the composition of these normal intestinal juices roughly corresponds with the fluid found in the fæces.

It should not be forgotten that inflammatory transudation from the intestines may result, especially after large doses of purgatives belonging to the drastic group. This effect is the same as that which is obtained on any other mucous surface or the skin by the action of irritants; it is shown here by the tenderness of the abdomen, redness and congestion of the mucous membrane, and exudation of a muco-purulent fluid which is often blood-stained. In the case of the intestines such an effect is never one to be desired for therapeutic purposes.

The increased peristalsis is caused by direct irritation of the intestines. The epithelial cells appear to take up a minute amount of the irritant drug, which acts as a powerful stimulus to the peripheral sensory endings in these cells. A local reflex occurs through the nerve-cells in Auerbach's plexus, leading to augmented peristalsis (Fig. 73). The reflex is a local one, since irritant purgatives increase the peristalsis of an isolated loop of gut. And the effect is not specific, as very little, if any, of the active substance is absorbed into the system. Nevertheless, certain of the vegetable purgatives augment peristalsis when injected subcutaneously or intravenously. Such is the case with senna, aloin, colocynth, and podophyllotoxin; this effect could only be produced if either they acted in a specific fashion through the circulation or were excreted into the gut, and so caused their ordinary irritant action. Both these effects probably occur, but especially the latter. This can be illustrated by injecting some cathartic drug subcutaneously into a cat or dog, when purging occurs in from half an hour to two hours, sometimes accompanied by vomiting. If the animal is killed four

or five hours later, the intestine from the jejunum to the rectum is found inflamed, and from the lumen the purgative drug can be extracted by chemical means. Every irritant substance injected under the skin behaves as a purgative.

The vegetable purgatives vary in the time they require for their action, but it is generally from five to ten hours. Large quantities of certain very powerful purgatives, such as croton oil, may act within two hours, whilst others, such as podophyllin and aloes, take as long as twelve hours.

The presence of bile is important for the action of some purgatives. Thus, podophyllin, jalap, rhubarb, and senna lose most of their activity when the bile duct is clamped. The bile apparently acts by altering their solubility, because if they are administered along with soaps their activity returns.

Besides these effects on the alimentary canal the vegetable purgatives have certain secondary actions. They increase reflexly the peristaltic movements of the uterus, and so are emmenagogues; whilst large doses of drastic purgatives administered to pregnant women may induce abortion.

Purgation lowers the blood-pressure, first, by withdrawing a quantity of fluid from the system which would otherwise be absorbed and excreted in the urine; and, secondly, by relieving pressure on the abdominal veins. The vegetable purgatives should not be absorbed; but if absorption occurs as the result of some abnormal condition, inflammation of the kidneys occurs and is associated with pain in the back and the typical urinary signs of acute nephritis.

Action of Saline Purgatives

Saline purgatives act in an entirely different manner from the vegetable purgatives in that their local irritant action on the bowel is insignificant. It was formerly taught that saline purgatives excited more or less secretion from the alimentary canal, while the low diffusibility of the salt impeded the absorption of the secreted fluid: it was therefore recommended that salines should be given in concentrated solution. That this is wrong is shown from the fact that the purgative action of the various salts is in no way proportional to their endosmotic equivalent.

Saline substances are not absorbed at the same rate; some are rapidly taken up from the stomach and small intestines, and others more slowly, so that they may reach the large intestine before any appreciable absorption has occurred. The kations potassium, sodium, and lithium are absorbed about equally rapidly from the small intestine, calcium more slowly, and magnesium the slowest of all. Of the anions, chlorides are the most rapidly absorbed, then follow bromides, iodides, nitrates, and, lastly, sulphates, the latter being excreted almost entirely by the rectum. Now the cathartic action of an ion depends on the time required for its

absorption. The slower the absorption the greater is the purgative effect; for example, both ions in potassium chloride are rapidly absorbed, and the salt is not cathartic. Magnesium chloride is, however, an active purgative, and the cathartic action in this case must, therefore, depend on the kation, as the Cl ion has already been shown to be inactive. But catharsis can also be obtained with the anion, because such substances as sodium sulphate and potassium tartrate are purgatives, although neither the potassium nor sodium produces the effect. It is obvious from these facts that magnesium sulphate should be an excellent cathartic, because in this body neither ion is rapidly absorbed and both are free to exert their effect. As the result of their being non-absorbable these soluble salts exert their osmotic properties. First, they increase the amount of liquid in the alimentary canal. Thus, if an isotonic solution of magnesium sulphate is injected into a loop of intestine (Fig. 70), very little absorption or secretion goes on, and in three hours' time the same amount of salt and fluid can be obtained. In stronger solutions they are the means of withdrawing fluid from the surrounding tissues. This can be shown also by the loop of Moreau: the fluid, however, so exuded is not an exudation from the vessels, for it contains no proteid, and the effect is entirely osmotic. The presence of these salts in the gut prevents the absorption of fluid, which would otherwise be taken up by the tissues, and hence a much larger amount of liquid will reach the large intestine, and the contents of the bowel will necessarily be more fluid. This increase in the fluid, and the consequent distension, will produce some increased peristalsis, and there is an almost uniform passage of the fluid motion throughout the whole intestinal tract.

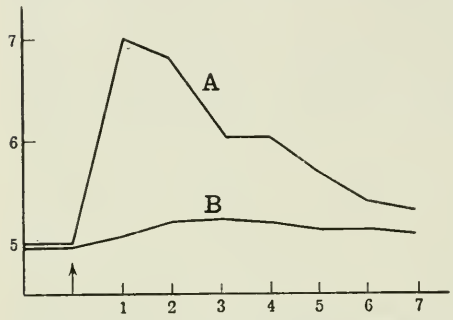


FIG. 71.—TWO CURVES SHOWING NUMBER OF RED BLOOD CELLS IN A NORMAL MAN.

Ordinates = number of red cells per cubic millimetre blood. Abscissa = time in hours. At the arrow the man received 6 drachms sodium sulphate in a 25 per cent. solution (curve A), and on another occasion as a 5 per cent. solution (curve B). The concentrated solution removes water from the blood, and the purgative action is not obtained till 12 to 18 hours. The more dilute solution does not alter the water content of the blood, but purgation follows in an hour or two.

It must be noted that although isotonic and hypotonic solutions of cathartic salts will act as purgatives by retarding absorption, yet it is only hypertonic solutions which extract water from the blood, and these salts may fail to purge if the blood and tissues contain very little fluid, as has been shown in the case of animals which have been deprived of water for a few days previously; on the contrary, where large quantities of fluid are present in the

system, as in dropsy, the saline cathartics, especially when administered in a concentrated form, drain the water indirectly through the blood into the bowel.

An attempt has been made to explain the selective action of the intestinal epithelium in allowing certain ions to permeate freely and refusing admission to others, by the fact that the purgative ions have a greater tendency to precipitate proteins and less tendency to permeate into unorganised colloids than most of the non-purgative salts.

Before leaving the subject of saline purgatives, it should be noted that magnesium sulphate, injected subcutaneously in small doses (5–10 grs.), produces a cathartic action. This effect bears no relationship to saline action, but is caused by the irritant action of the magnesium during its excretion into the gut.

Purgative Oils

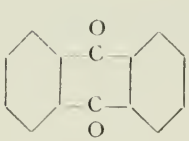
Castor oil is obtained by expression from the seeds of *Ricinus communis*. It is principally composed of a mixture of the glycerides of ricinoleic acid and its isomer. Ricinoleic acid is responsible for the purgative effect, but no acid is present in normal oil, and it is not till it has been saponified in the duodenum that its action is exerted. This substance is probably a hydroxyl derivative of oleic acid, and has the formula $C_{17}H_{32}(OH).COOH$. Like olive oil it may be used as an emollient. Ricinone, a purgative substance, and ricin, a poisonous protein, are contained in the seed, but neither occurs in the oil. If the oil is saponified before being given by the mouth the effect of the free acid is obtained immediately, and an action apparently different from that of the oil is obtained: it is acrid and unpleasant to the taste, and nausea and vomiting may result from its direct action on the stomach. Castor oil may be given in large quantities without producing any symptoms save those of a laxative. It acts upon the small intestine, and not on the large bowel.

Croton oil is obtained by expression from the seeds of *Croton tiglium*. It consists of a mixture of various free fatty acids and their glycerides. The active ingredient is a resinous body, $C_{13}H_{18}O_4$, croton resin, which is a powerful vesicant. Croton oil is infinitely more toxic than castor oil, one minim being a full dose for a man, and as its active ingredient is free in the oil, it obviously exerts its effect on the stomach as well as the intestines.

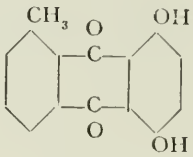
Anthracene Purgatives

Anthracene purgatives form a distinct group, and include rhubarb, senna, aloes, and cascara. They are mild in action, and never produce the acute inflammation of the intestines which is so marked a feature of excessive doses of the drastic group. These bodies are

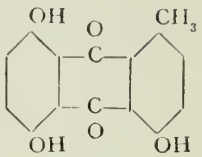
mainly derived from anthraquinone by the substitution into the ring of OH and CH_3 groups.



Anthraquinone.



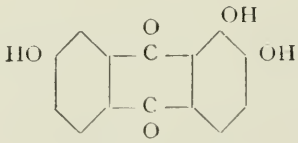
Chrysophanic acid.



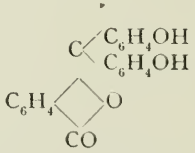
Emodin.

Each of the drugs mentioned contains a number of these bodies, all more or less related to one another, partly free, but mainly as glucosides, which do not act as purgatives until they are decomposed in the intestines. Owing to this gradual liberation of active principle they act mainly on the large intestine and are especially useful in chronic constipation. A small percentage of the anthracene purgatives is absorbed from the intestines into the blood and is excreted by the urine, to which some of them, rhubarb and senna, impart a yellowish-brown colour, which turns purplish-red when alkali is added. The fact that with large doses the absorption may be considerable, even leading to inflammatory conditions of the kidney, is the principal drawback to the use of this group, for otherwise they possess ideal purgative properties, in that they have little effect on the stomach and do not give rise to inflammatory conditions in the small intestines.

A number of synthetic anthracene bodies have of late years been suggested as substitutes for the crude drugs, but experimental results with these substances show little to recommend them, much of their purgative action is lost, whilst their absorption is increased; for example, aloin is not so effective as aloes, and chrysophanic acid, when pure, is no longer a purgative owing to its very rapid absorption.



Anthrapurpurin.
Purgatin is the diacetate.



Phenolphthalein.
Purgen.

Purgatin produces semi-solid motions in from eight to twelve hours after doses of 25 grs. It also causes back-ache and stains the urine red. *Purgen* (phenolphthalein) is insoluble in water but soluble to about 2 per cent. in olive oil, and causes loose motions in from four to six hours. Unlike purgatin it is not absorbed in appreciable amounts, but occasionally it produces albumin and

free hæmoglobin in the urine. Solutions in oil injected subcutaneously cause purgation without local irritation.

Rhubarb is the dried root of *Rheum palmatum*. It contains a large number of anthracene bodies, especially chrysophanic acid, emodin, and a body closely resembling the cathartic acid of senna, to which its purgative action is mainly due. Besides these there is a considerable amount of tannin present, which is said to be responsible for the constipation that usually follows the effect of the drug. A small amount of the anthracene bodies is absorbed and secreted in the urine, staining it yellow, which turns to red on the addition of alkali.

Senna.—The dried leaflets of *Cassia acutifolia*. The drug contains several anthracene bodies, including emodin, chrysophanic acid, and cathartic acid, and to this last the purgative action is mainly due. Cathartic acid is probably not a pure substance, but it has been given the provisional formula $C_{30}H_{36}NO_{15}$. The urine is stained yellow. Senna does not cause subsequent constipation like rhubarb. Study by means of the Röntgen rays shows that the action of senna is confined to the peristalsis of the colon ; it has no influence on the movements of the stomach or of the small intestine. As soon as the infusion of senna reaches the cæcum and the ascending colon complete evacuation of the colon takes place, and this evacuation is repeated several times so long as any of the senna remains in the colon or in the cæcum.

Cascara is the dried root of *Rhamnus purshianus*. Emodin and frangulic acid are the principal anthracene constituents. The drug slowly loses its purgative properties on keeping. One advantage of its use is stated to be that continually increasing doses are not required.

Aloes is obtained by evaporating the juice which flows from the transversely cut leaves of various species of Aloe. Some is imported from Barbados and Curaçao, and another variety from Sokotra and Zanzibar ; but the main effect of the drug wherever obtained is the same. The bitter crystalline principles obtained from all species of aloe are known under the generic name of aloin, and this consists of a number of anthracene derivatives which have not yet been completely identified. The purgative action is increased by the simultaneous administration of small quantities of alkaline salts and of iron. Aloes will not produce an efficient action in the absence of bile, and an enema of aloes is without action unless bile is also injected ; but certain other bodies, such as glycerine, which also exert a solvent action, may be efficiently substituted for the bile. Aloes exerts its full action low down on the large intestine like senna. Its action on the rectum induces reflex uterine contractions, and hence this drug is an indirect emmenagogue.

Drastic Purgatives

These bodies are mostly of uncertain composition : some contain glucosides, as colocynth and jalap, and others bitter principles neither acid, glucosidal, nor alkaloidal in nature, such being elaterium and podophyllum. These drugs are much more irritant than the anthracene group, and large doses readily set up acute inflammation of the stomach and intestines, with violent peristaltic contractions,

and exudation of muco-purul nt material, which is sometimes blood-stained. After such doses it is not uncommon to see acute inflammation of the kidneys and bladder. In therapeutic doses the drastic purgatives act more rapidly than the anthracene purgatives, but their irritant action is not confined to the intestines, and nausea and vomiting often occur. In about three hours the contents of the small intestine are discharged. The normal cæcal activity is absent and the rapid passage through the large intestine of the fluid motion is characterised by repeated filling and sudden emptying of the ampulla (jalap and colocynth).

The irritant action can be shown on the skin and mucous membranes of the eye, nose, and throat, especially with podophyllin, jalap, and colocynth.

Most of these bodies produce nausea, vomiting, and diarrhœa when injected subcutaneously or intravenously, and enteritis and nephritis occur as when administered by the mouth.

Jalap consists of the dried tubercles of *Ipomœa purga*, and from these jalap resin is extracted by means of alcohol. The resin consists mainly of two glucosides, jalapin 90 per cent. and scammonin 10 per cent., which are closely allied to one another. But the latter alone is soluble in ether. After large doses no glucoside has been discovered in the urine. Bile is necessary for its action.

Scammony is a resin obtained by incision of the living root of *Convolvulus scammonia;* it exudes as a gummy substance, which is allowed to dry. Scammony resin is extracted from the root by alcohol. It is composed almost entirely of the glucoside scammonin, which is found also in jalap.

Podophyllin consists of the dried rhizomes of *P. peltatum*. Podophyllin resin is extracted by alcohol, and consists of active and inert substances. The active substances are podophyllo-toxin, a neutral crystalline substance, and a crystalline resin, podophyllo-resin. Both these bodies are active purgatives, and about equally toxic; both produce purgative effects when injected subcutaneously, but the resin only acts as a cholagogue. Subcutaneous injections produce violent purgation in from half to one hour, acute inflammation of the kidneys, and sometimes hæmorrhage into the bladder. Ulceration at the seat of injection is usual.

Colocynth is the fruit of *Citrullus colocynthis* freed from its rind and seeds. The bitter principle is an amorphous yellow glucoside, colocynthin (about 6 per cent. in pulp). Subcutaneous injections produce effects similar to those of podophyllin.

Euonymus, the dried root of *Euonymus atropurpureus*. It contains an amorphous bitter glucoside, euonymin, soluble in water and alcohol. It increases slightly the amount of bile and the bile salts. Euonymin has a digitalis-like action on the heart.

Gamboge.—A gum-resin obtained from *Garsinia Hanburii*. It contains more than 70 per cent. of gambogic acid, a bright yellow resin.

Enemata are injections into the rectum. They may be divided into two classes: (*a*) **nutrient**, consisting of food material; these

should not exceed three ounces, and should be injected at body temperature; and (*b*) **cathartic**, which also may be divided into two classes. The big enema consists of a pint or two of fluid, and acts partly by distension, which induces peristaltic contraction, and partly

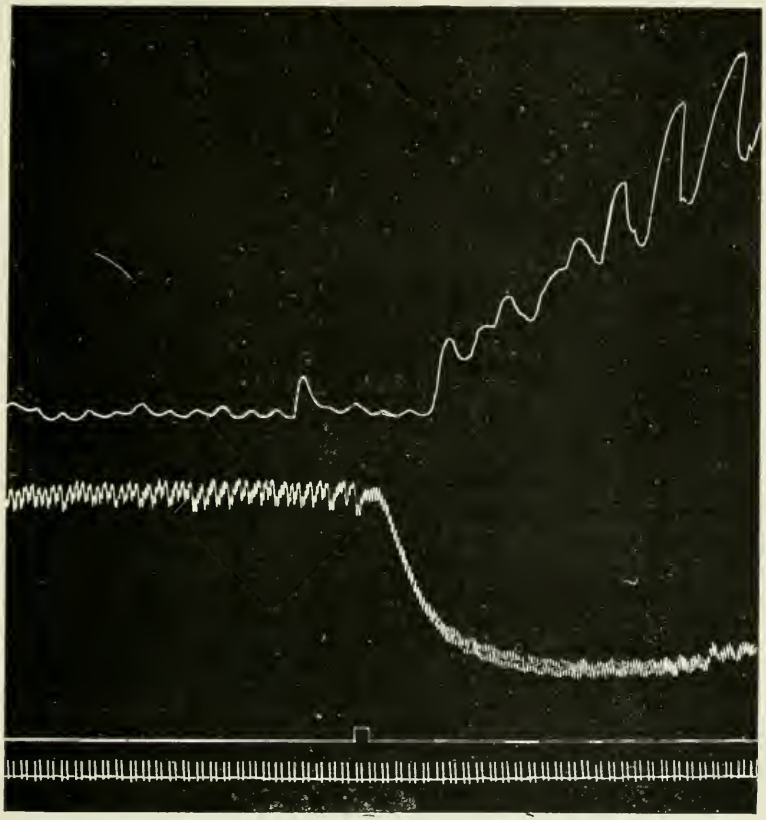


FIG. 72.—CAT. INTESTINAL MOVEMENTS AND BLOOD-PRESSURE.

The intestines were recorded by the balloon method. Shows the effect of injecting into the circulation 1 c.c. of a ½ per cent. solution of pilocarpine nitrate. Note the increased tonus and waves in the intestine. The fall of blood-pressure is due to vagal inhibition. Time = secs.

by softening the scybala. Warm water will produce this effect alone, but the action can be increased by using cold water or adding some irritant substance to the water, such as soap, salt, or turpentine. It is probable that these irritants induce, reflexly, contractions in the upper part of the rectum, to which they never gain access.

The small cathartic enema consists of an injection of from one to three ounces of fluid, and contains colocynth, aloes, or some other irritant purgative. They act much more rapidly than when given by the mouth, usually in from one to three hours.

Other Purgative Drugs not used as such.—Many other drugs produce evacuation of the bowel in the course of their action, but have other more important effects, and are not employed as purgatives. Thus, all skin irritants have a purgative action, which is accompanied by irritation of the mucous membrane of the mouth, throat, and stomach. The whole of the digitalis group of drugs is purgative. In this case the effect is principally produced after absorption, and is due to stimulation of the peripheral motor mechanism. Euonymin, a member of the digitalis group, is used for its purgative properties.

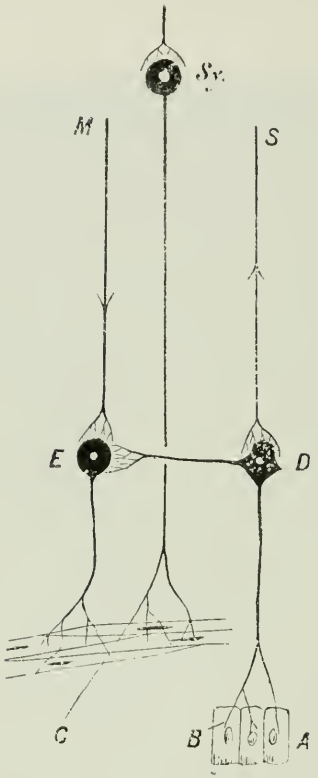


FIG. 73.—HYPOTHETICAL DIAGRAM TO EXPLAIN THE ACTION OF DRUGS ON THE INTESTINE. (*See Note.*)

A = mucous membrane, *B* = sensory nerve-endings, *C* = motor nerve-endings in muscle, *D* and *E* = nerve-cells in Auerbach's plexus, *M* = motor fibre from vagus, *S* = sensory fibre, *Sy* = sympathetic nerve-cell in the solar ganglion.

Probable Seat of Action of Drugs.

B.—Vegetable purgatives + and produce a local reflex through *D* and *E*.
Sy. Endings in muscle.—Adrenalin +.
Sy. Cells.—Nicotine + −, Coniine + −, Lobeline + −, Gelsemine −, certain opium-alkaloids − (Depression of these cells increases peristalsis).
D.—Morphine −.
C.—Pilocarpine +, Physostigmine +, Colchicine +, Digitalis +, Atropine −.
Muscle.—Heavy metals such as Lead and Barium, or Veratrine +.

NOTE.—Sensory fibres no doubt go directly upwards without the intervention of a sensory cell at *D*: and *D* may not exist, but lateral fibres from the sensory nerve may form arborisations round *E*.

Pilocarpine, physostigmine, and colchicine cause increased peristaltic movements and diarrhœa by direct stimulation of peripheral motor mechanism, and the effects can be in each case antagonised by means of atropine (Fig. 72).

Finally, in large doses almost all the alkaloids of opium give rise to increased peristalsis, especially when injected subcutaneously. This action is generally accompanied by vomiting, and is more pronounced with codeine and apomorphine than morphine. It is, however, best seen with apocodeine, when vomiting is generally absent. Apocodeine produces its effect by paralysing the peripheral inhibitory nerve mechanism. Thus, Fig. 73 shows a possible arrangement of

the peripheral nervous mechanism in the intestines. *M* represents the motor fibres of the vagus, the endings of which at *C* are partially paralysed by atropine, and excited by pilocarpine, physostigmine, colchicine, and digitalis. Atropine paralyses some portion of the nerve-endings, but only a portion, for excitation of the vagus nerve is still effective after atropine. The ordinary irritant purgative excites the sensory endings *B*, and so augments peristalsis reflexly through the nerve-cells *D* (?) and *E*. Atropine relieves the pain of griping without hindering peristalsis; and it may be regarded as paralysing, in part only, the sensory nerve-endings at *B* or *D*.

Cholagogues

It has long been assumed that the majority of the vegetable purgatives stimulate the liver and increase the secretion of bile. This is now known in the majority of cases to be untrue; the supposed cholagogue action is caused by the more rapid movements of the contents of the gut, so that sufficient time is not allowed for the absorption of the bile constituents, which are, therefore, found in greater amount in the fæces. In some cases there is contraction of the gall-bladder, which would exaggerate the fallacy.

A cholagogue is generally defined as a substance which increases the secretion of bile, and as the bile salts usually keep pace with the secretion, the amount of fluid can be accepted as a rough estimate of cholagogue action. It would always be more accurate to estimate both the quantity of bile and the percentage of salts.

The methods which have been adopted for determining cholagogue action consist of (1) permanent fistulæ (man and animals). The diet, exercise, and all external surroundings should be kept as constant as possible, and when the secretion of bile has been steady for some days the cholagogue may be administered, and the bile examined during the next twenty-four hours. (2) The second method consists of tying a cannula into the bile duct of an anæsthetised and curarised dog in which the cystic duct is clamped, and measuring the secretion per minute before and after the injection of the cholagogue into the duodenum.

By experiments of this nature the following conclusions have been arrived at:—Water, even in large amounts, does not alter the quantity of bile; thus, the secretion rather resembles that of a salivary gland than of the kidney. By far the surest and most powerful cholagogue we possess is bile itself or the bile salts; it produces a rapid increase of secretion, which lasts over twenty-four hours, and the larger the dose administered the larger the secretion, the liquid and solid constituents being increased proportionally.

A number of other bodies possess a moderate cholagogue effect: these include turpentine, sodium benzoate, sodium salicylate, euonymin, and podophyllo-resin; the latter drug is remarkable in that it is stated to increase the bile salts without affecting the

volume of the secretion. At present it is not possible to indicate any condition in which the administration of cholagogues is desirable, and the suggestion that they might be used to overcome biliary obstruction cannot be entertained, as even a slight increase of pressure is sufficient to inhibit all flow. Bile has the power of increasing the action of some purgatives—podophyllin, jalap, rhubarb, senna, and aloes. This may be due to the physical action of the bile, because soaps given with these drugs appear to subserve the same effect as the bile.

Fel Bovinum is employed in medicine in those cases where there is reason to believe that there is a deficiency in the bile salts. It would be especially indicated in biliary fistula, since in such a case the bile salts are permanently lost, whilst under normal conditions, after serving their purpose in the duodenum, they are re-absorbed, and so continue to move in a circle. The bile salts assist in the emulsification of fats, and act as mild antiseptics and purgatives.

MATERIA MEDICA

Laxatives :—

Tamarindus.—Contains about 15 per cent. of tartrates and citrates. **Dose, ½ to 1 oz.**

Cassiæ Fructus.

Cassiæ Pulpa.—Contains about 60 per cent. of a sugar.

Oils :—

Oleum Ricini. Dose, 1 to 8 drs. (4 to 30 mils).

PREPARATION

Mistura Olei Ricini.—Contains 3 drs. of castor oil in 1 oz.
Dose, 1 to 2 oz. (30 to 60 mils).

Oleum Crotonis. Dose, ½ to 1 m. (3 to 6 centimils). On dry sugar or mixed with butter.

PREPARATION

Linimentum Crotonis.—1 in 8.

Anthracene Group :—

Rhei Rhizoma. Dose, 3 to 10 grs. (2 to 6 dcgrms.), or up to **30 grs.** (2 grms.) for a single administration.

PREPARATIONS

1. **Extractum Rhei.**
   Dose, 2 to 8 grs. (12 to 50 ctgrms.).
2. **Infusum Rhei.**
   Dose, ½ to 1 oz. (15 to 30 mils).
3. **Pilula Rhei Composita.**—Rhubarb, aloes, myrrh and peppermint.
   Dose, 4 to 8 grs. (25 to 50 ctgrms.).
4. **Pulvis Rhei Compositus.**—Gregory's powder : rhubarb, light magnesia, and ginger.
   Dose, 10 to 60 grs. (6 to 40 dcgrms.).

5. Syrupus Rhei.
   Dose, ½ to 2 drs. (2 to 8 mils).
6. Tinctura Rhei Composita.
   Dose, ½ to 1 dr. (2 to 4 mils) (repeated administration); 2 to 4 drs. (8 to 16 mils) (single administration).

Senna.
Sennæ Fructus.
Sennæ Folia.

PREPARATIONS

1. Confectio Sennæ.
   Dose, 60 to 120 grs. (4 to 8 grms.).
2. Infusum Sennæ.
   Dose, ½ to 1 oz. (15 to 30 mils).
3. Mistura Sennæ Composita.—Black draught: magnesium sulphate, extract of liquorice, aromatic spirit of ammonia, infusion of senna.
   Dose, 1 to 2 ozs. (30 to 60 mils).
4. Pulvis Glycyrrhizæ Compositus.
   Dose, 60 to 120 grs. (4 to 8 grms.).
5. Syrupus Sennæ.
   Dose, ½ to 2 drs. (2 to 8 mils).
6. Tinctura Sennæ Composita.
   Dose, ½ to 1 dr. (2 to 4 mils) for repeated administration; 2 to 4 drs. (8 to 16 mils) for single administration.

Cascara Sagrada.

PREPARATIONS

1. Extractum Cascaræ Sagradæ Siccum.
   Dose, 2 to 8 grs. (12 to 50 ctgrms.).
2. Extractum Cascaræ Sagradæ Liquidum.
   Dose, ½ to 1 dr. (2 to 4 mils).
3. Syrupus Cascaræ Aromaticus.
   Dose, ½ to 2 drs. (2 to 8 mils).

Aloe. Dose, 2 to 5 grs. (12 to 30 ctgrms.).

PREPARATIONS

1. Extractum Aloes.
   Dose, 1 to 4 grs. (6 to 25 ctgrms.).
2. Decoctum Aloes Compositum.
   Dose, ½ to 2 oz. (15 to 60 mils).
3. Pilula Aloes.
   Dose, 4 to 8 grs. (25 to 50 ctgrms.).
4. Pilula Aloes et Ferri.
   Dose, 4 to 8 grs. (25 to 50 ctgrms.).
5. Pilula Aloes et Asafetidæ.
   Dose, 4 to 8 grs. (25 to 50 ctgrms.).
6. Pilula Aloes et Myrrhæ.
   Dose, 4 to 8 grs. (25 to 50 ctgrms.).

Aloinum. Dose, ½ to 2 grs. (3 to 12 ctgrms).

Purgatin. (Not official.) Is the diacetate of anthrapurpurin. Dose, 15 to 30 grs.

Phenolphthalanum. Dose, 2 to 5 grs. (12 to 30 ctgrms.).

Drastic Purgatives :—

Jalapa. Dose, 5 to 20 grs. (3 to 12 dcgrms.).

PREPARATIONS

1. Pulvis Jalapæ Compositus.—Jalap, acid tartrate of potassium, and ginger.
   Dose, 10 to 60 grs. (6 to 40 dcgrms.).
2. Tinctura Jalapæ.—Standardised to contain 1.5 per cent. of jalap resin.
   Dose, ½ to 1 dr. (2 to 4 mils).
3. Tinctura Jalapæ Composita. Dose, ½ to 1 dr. (2 to 4 mils).

Jalapæ Resina. Dose, 2 to 5 grs. (12 to 30 ctgrms.).

Scammoniæ Radix.

Ipomœde Radix.

Scammoniæ Resina. Dose, 4 to 8 grs. (25 to 50 ctgrms.).

PREPARATION

Pulvis Scammonii Compositus.
Dose, 10 to 20 grs. (6 to 12 dcgrms.).

Podophylli Rhizoma.

Podophylli Resina. Dose, ¼ to 1 gr. (16 to 60 mgrms.).

PREPARATION

Tinctura Podophylli.
Dose, 5 to 15 m. (3 to 10 decimils).

Colocynthidis Pulpa.

PREPARATION

1. Extractum Colocynthidis Compositum. Also contains Barbados aloes and resin of scammony.
   Dose, 2 to 8 grs.
2. Pilula Colocynthidis Composita. Also contains aloes and resin of scammony.
   Dose, 4 to 8 grs. (12 to 50 ctgrms.).
3. Pilula Colocynthidis et Hyoscyami.
   Dose, 4 to 8 grs. (25 to 50 ctgrms.).

Euonymi Cortex.

PREPARATION

Extractum Euonymi. (Euonymin.)
Dose, 1 to 2 grs. (6 to 12 ctgrms.).

Gambogia. Dose, ½ to 2 grs. (Not official.)

Iridin. (Not official.) Dose, 1 to 3 grs.

Fel Bovinum Purificatum. Dose, 5 to 15 grs. (3 to 10 dcgrms.).

VEGETABLE ASTRINGENTS

A considerable number of vegetable drugs contain tannic acid, and some of these are used in medicine entirely on account of the presence of this body. These drugs may be classified in one group, and spoken of as the vegetable astringents. When applied to the tongue they cause a feeling of constriction, roughness, and dryness, and give rise to a characteristic "astringent" taste. There is a visible wrinkling of the mucous membrane to which they are applied, and a diminution in the secretion of mucus. These effects are due to the direct chemical action of tannin on proteid.

The tannins are mostly anhydro-acids derived from benzoic acid by condensation, and several of them exist in the plant as glucosides. The tannic acid usually employed in medicine is prepared from oak gall-nuts, and has the formula $C_6H_2(OH)_3CO.O.C_6H_2.(OH)_2COOH$. The tannins prepared from other plants, while not chemically identical with oak-tannin, possess the same pharmacological action. Tannic acid is readily decomposed into gallic acid.

$$\underset{\text{Tannic acid.}}{C_6H_2(OH)_3.CO.O.C_6H_2(OH)_2COOH} + OH_2 = 2\underset{\text{Gallic acid.}}{C_6H_2(OH)_3COOH}.$$

As the pharmacology of the tannins depends upon their chemical interaction with proteids and gelatin, this will be considered in detail.

Chemical Action.—Tannins possess a strongly acid reaction, and are very soluble in water and dilute alcohol.

A solution of tannin added to albumen or gelatin produces a dense greyish-white precipitate, which is soluble in excess of albumen, gelatin, acetic acid, lactic acid, or the alkalies, including the alkaline carbonates.

With connective tissue it forms an exceedingly insoluble compound, leather.

Peptones and pepsin are precipitated in neutral media only. Tannic acid behaves in virtue of its acid radicle, and when this is neutralised with an alkali, or by the addition of albumen so as to form an albuminate, its astringent properties are no longer exerted. Hence, alkaline tannates have no effect on albumen or gelatin, although they still retain an "astringent" taste; they can, in fact, no longer be classified as true astringents. Ferric chloride, with solutions of the acid, gives a bluish-black precipitate soluble in dilute sulphuric acid, and reprecipitated by the addition of ammonia.

Tannic acid added to many of the salts of the alkaloids forms a precipitate which is soluble in acetic acid. Hence, it is used as an antidote in cases of alkaloidal poisoning when the alkaloid is still present in the stomach.

It also precipitates some glucosides and certain salts of the heavy metals.

Effect on the Alimentary Canal.—Reference has been made to the action of tannin in the mouth. It coagulates proteid material surrounding the epithelium, and even penetrates some of the superficial epithelial cells. The feeling of astringency, the dryness, stiffness, and drawing together experienced in the mouth, are continued in the throat. On reaching the stomach, which, let us say, contains food, tannin combines with any alkali or proteid present and forms a tannate, and thus for the time being it loses its astringent properties. The tannate of albumen so formed undergoes digestion like any other coagulated protein, and the tannin is again liberated and free to re-combine. The pepsin and peptones are not affected on account of the free hydrochloric acid. The astringent action of tannin may be continued some distance along the small intestine; the drug can be recognised by the ferric chloride test. Its presence here tends to produce constipation, first, by coagulation of proteids, and, secondly, on account of the diminution in mucous and other glandular secretions. Tannin acts in a mild degree as an antiseptic, and makes the fæces less offensive; but in this action it cannot be compared with the other and more usually recognised antiseptics such as those of the coal-tar group.

When administered on an empty stomach its effects are naturally more pronounced, and it sometimes causes objectionable irritant effects, as shown by vomiting or even diarrhœa.

Absorption and Secretion.—Tannic acid administered by the mouth is destroyed by oxidation and disappears entirely. Only about 1 per cent. of that taken can be recovered either from the urine or fæces, and this is present almost wholly in the form of gallates. If dogs are dosed with tannin little or none can be detected in the blood, and the urine contains only the merest trace, although gallic acid can be found in both. Similarly the fæces contain gallic acid, and tannin is difficult to detect.

In man the same result is obtained, and even after large doses of tannin it is not easy to detect it in the urine, although gallic acid is present. It therefore appears that such tannin as is absorbed into the system is taken up as alkaline gallates, that this circulates in the blood and is excreted in the urine, mere traces of alkaline tannates being present.

If, instead of tannic acid, an alkaline tannate is administered the results are somewhat different, for this salt is rapidly absorbed and quickly appears in the urine. It should always be remembered that such salts (alkaline tannates) are comparatively inert, and, like gallic acid, have no affinity for either protein or gelatin. The urine when voided is normal in appearance, but darkens on standing from the formation of pyrogallic acid. There may be some slight diuresis.

Specific Effect.—It must be remembered that only a very small amount of tannin is absorbed, and that this is almost entirely in the form of alkaline gallate; hence the injection of tannic acid

into a vein is not a fair means to determine the specific action of the drug as given by the mouth.

Tannic, gallic, and pyrogallic acids, when applied directly to the mesentery of curarised frogs, produce vaso-dilatation, but there is no evidence to show that any such effect may be produced in mammalia by the comparatively small amount of gallates which are absorbed. Certainly vaso-constriction does not occur, and the vegetable astringents never produce this effect. Other specific actions have been described, such as contraction of the splenic muscle, and an effect on voluntary muscle, but the results are very doubtful and of no practical importance.

Gallic acid is found free in gall-nuts, China tea, and other astringent vegetables. It is prepared by fermenting the tannic acid contained in gall-nuts, and behaves with ferric chloride in the same way as tannin and tannates; but, as already shown, it has no effect on albumen or gelatin and has no astringent properties. Gallic acid heated to 230° produces pyrogallic acid, which in alkaline solutions absorbs oxygen.

Other astringents, the action of which is dependent on the presence of tannin, are the following :—

Catechu is an extract prepared from the leaves and young shoots of *Uncaria gambier*. Its chief constituents are 7 to 33 per cent. catechin, which bears a considerable analogy to gallic acid in its behaviour to metallic salts, and 22 to 50 per cent. of catechu-tannic acid.

Rhatany.—The root of two species of Krameria. It contains about 8.4 per cent. of rhatania-tannic acid, which resides in the bark. It also contains a colouring matter which is a decomposition product of the tannin.

Kino is the evaporated juice from the trunk of *Pterocarpus marsupium*. It contains from 70 to 80 per cent. of kino-tannic acid, and about 1.5 per cent. of kinoin, a colourless crystalline substance.

Logwood contains 10 per cent. of a red-coloured crystalline body, hæmatoxylin, which yields pyrogallol when fused with alkalies. Hæmatoxylin has neither bitterness nor astringency, but both these properties develop by oxidation as a result of keeping ; and a body named hæmatein is formed. Logwood also contains tannic acid. One disadvantage of this substance is that it stains linen.

Hamamelis.—The bark and leaves of the witch-hazel. It contains about 6 per cent. of tannin as well as gallic acid, a bitter principle, and a volatile oil.

The tannin is partly crystalline and partly amorphous.

Kino Eucalypti is a ruby-coloured exudation from the bark of *Eucalyptus rostrata*. The gum contains 40 per cent. or more tannic acid, as well as catechin, pyrocatechin, kino-red, and gum.

Unofficial

Diacetyl tannin or *tannigen* was introduced with the view that it would pass through the stomach unchanged and without producing any local astringent action. The change into tannic acid takes place in part only. Dose, 5 to 10 grs.

Methyl ditannin or *tannoform* is perhaps a better preparation which also passes unchanged through the stomach, but is split up in the duodenum, tannic acid being liberated. Dose, 5 to 15 grs. Both these substances are insoluble until they are broken down by alkalies; they are employed in the treatment of chronic diarrhœa.

MATERIA MEDICA

Galla (Galls).

Preparations

1. **Unguentum Gallæ.**
2. **Unguentum Gallæ cum Opio.**—7½ per cent. opium.

Acidum Tannicum. Dose, 5 to 10 grs. (3 to 6 decgrms.).

Preparations

1. **Glycerinum Acidi Tannici.**—1 in 5.
2. **Suppositoria Acidi Tannici.**—3 grs. in each
3. **Trochiscus Acidi Tannici.**—½ gr. in each.

Catechu. Dose, 5 to 15 grs. (3 to 10 decgrms.).

Preparations

1. **Pulvis Catechu Compositus.**—Contains kino and krameria. Dose, 10 to 60 grs. (6 to 40 decgrms.).
2. **Tinctura Catechu.** Dose, ½ to 1 dr. (2 to 4 mils).
3. **Trochiscus Catechu.**—1 gr. in each.

Krameriæ Radix (Rhatany).

Preparations

1. **Extractum Krameriæ.** Dose, 5 to 15 grs. (3 to 10 decgrms.).
2. **Infusum Krameriæ.** Dose, ½ to 1 oz. (15 to 30 mils).
3. **Pulvis Catechu Compositus.** Dose, 10 to 60 grs. (6 to 40 decgrms.).
4. **Tinctura Krameriæ.** Dose, ½ to 1 dr. (2 to 4 mils).
5. **Trochiscus Krameriæ.**—1 gr. in each.
6. **Trochiscus Krameriæ et Cocainæ.**—1 gr. and $\frac{1}{20}$ gr. in each.

Kino. Dose, 5 to 20 grs. (3 to 12 decgrms.).

Preparations

1. **Pulvis Kino Compositus.**—1 of opium in 20. Dose, 5 to 20 grs. (3 to 12 decgrms.).
2. **Tinctura Kino.** Dose, ½ to 1 dr. (2 to 4 mils).
3. **Pulvis Catechu Compositus.**

Hæmatoxyli Lignum.

Preparation

Decoctum Hæmatoxyli. Dose, ½ to 2 oz. (15 to 60 mils).

Hamamelidis Cortex.

Preparation

Tinctura Hamamelidis. Dose, ½ to 1 dr. (2 to 4 mils).

Hamamelidis Folia.

PREPARATIONS

1. Extractum Hamamelidis Liquidum. Dose, 5 to 15 m. (3 to 10 decimils).
2. Liquor Hamamelidis.
3. Unguentum Hamamelidis.

Kino Eucalypti. Dose and action like Kino.

PREPARATION

Trochiscus Kino Eucalypti.—1 gr. in each.

SIMPLE BITTERS

The simple bitters comprise a large collection of drugs of vegetable origin which possess little in common except their bitter taste. They are mostly of unknown composition, and we are unable at present to suggest any relationship between the bitter sensation and their chemical composition. They can be administered freely without fear of ill effects, and are not toxic except in enormous doses.

Many drugs possess a bitter taste, but they also have other and far more important actions which overshadow this particular property and demand their fuller consideration elsewhere; for example, most of the alkaloids, such as morphine, strychnine, and quinine, are extremely bitter, as well as other bodies, aloes and rhubarb, all of which during the course of their action would exert the ordinary properties of the bitters. The drugs which find a place in the British Pharmacopœia on account of their bitter properties are the following:—

Gentian.—The root of the yellow gentian. It contains 0.1 per cent. of a crystalline glucoside, gentiopicrin, to which its bitter properties are mainly due.

Quassia.—The wood obtained from *Picræna excelsa*. Its activity depends on a mixture of homologous, crystalline bitter principles termed picrasmin.

Calumba.—The root of *Jateorhiza Calumba*. It contains three crystalline bitter principles, calumbic acid, its anhydride calumbin, and the alkaloid berberine.

Chirata is the dried plant *Swertia chirata*. It contains ophelic acid, and a crystalline bitter principle, chiratin, which is decomposed by acids into ophelic acid.

Taraxacum.—The root of the dandelion. The active principle is a crystalline substance called taraxacin.

Cascarilla is the dried bark of *Croton eluteria*. The bitter principle is a crystalline alkaloid cascarilline.

Serpentaria.—The rhizome of *Aristolochia serpentaria*. It contains a bitter principle, aristolochine, and from 1 to 2 per cent. of a volatile oil.

Aurantii Cortex.—Dried or fresh bitter orange-peel. The chief constituent is a volatile oil. The bitter principle is an amorphous glucoside, aurantiamarin.

Action

Bitters are used to increase the appetite and benefit digestion. Clinically their value is beyond dispute, although their exact mode of action is not quite clear. When the pure bitters are added to artificial digestions going on outside the body, little effect is observed unless the quantity of bitter present is excessive, when the digestion is retarded; this is true for salivary, gastric, and pancreatic digestions.

It has been shown that bitters administered on an empty stomach first tend rather to diminish the secretion; this is succeeded in the course of about half an hour by a considerably augmented secretion, and in this fact consists the *rationale* of administering bitters half an hour before food. The cause of this secretion is not definitely known, but it is, partly at least, reflex in origin. Pawlow showed that in dogs with an œsophageal fistula, food administered by the mouth induced a copious gastric secretion, although no food reached the stomach but passed directly to the exterior by the opening in the œsophagus. The secretion must, therefore, in this case be reflex, due to stimulation of the nerve-endings of taste, and it is this stimulation of the gustatory nerve-endings which induces the flow of gastric juice.

We may regard as a general law the fact that anything which improves the appetite increases the flow of gastric juice. Experience tells us very certainly that the bitters have the closest connexion with the condition of the appetite, and if, as there can be no doubt, they increase the appetite, then we have in them the strongest of all stimuli to the gastric glands. The mechanism by which the appetite is improved is not easy to explain. People suffering from digestive disturbances invariably have a blunted or perverted taste; ordinary foods are tasteless to them, and may be even nauseous. In such conditions we give the gustatory apparatus a powerful stimulant. Experience again teaches us that this object is quickest attained by exciting a sharp and unpleasant impression; this by contrast awakens pleasant ones, or, at all events, there is no longer indifference. We, therefore, conclude that bitters increase the flow of gastric juice by improving the appetite.

Some of the bitters, such as gentian, calumba, cusparia, and chamomile, are sialagogues acting reflexly through the mouth. Another effect, and one the significance of which we know but little, is an increase of the white blood-corpuscles in the peripheral circulation. In continued doses certain of the bitters such as quassia act as irritants and cause vomiting and diarrhœa.

MATERIA MEDICA

Calumbæ Radix.

PREPARATIONS

1. Infusum Calumbæ.
   Dose, ½ to 1 oz. (15 to 30 mils).
2. Tinctura Calumbæ.
   Dose, ½ to 1 dr. (2 to 4 mils).

Gentianæ Radix.

PREPARATIONS

1. Infusum Gentianæ Compositum.
   Dose, ½ to 1 oz. (15 to 30 mils).
2. Tinctura Gentianæ Composita.
   Dose, ½ to 1 dr. (2 to 4 mils).
3. Extractum Gentianæ.
   Dose, 2 to 8 grs. (12 to 50 dcgrms.).

Quassiæ Lignum.

PREPARATIONS

1. Infusum Quassiæ.
   Dose, ½ to 1 oz. (15 to 30 mils).
2. Tinctura Quassiæ.
   Dose, ½ to 1 dr. (2 to 4 mils).

Chirata.

PREPARATIONS

1. Infusum Chiratæ.
   Dose, ½ to 1 oz. (15 to 30 mils).
2. Tinctura Chiratæ.
   Dose, ½ to 1 dr. (2 to 4 mils).

Taraxaci Radix.

PREPARATIONS

1. Extractum Taraxaci.
   Dose, 5 to 15 grs. (3 to 10 dcgrms.).
2. Succus Taraxaci.
   Dose, 1 to 2 drs. (4 to 8 mils).

Serpentariæ Rhizoma.

PREPARATION

Tinctura Serpentariæ.
Dose, ½ to 1 dr. (2 to 4 mils).

Cascarillæ Cortex.

PREPARATIONS

1. Infusum Cascarillæ.
   Dose, ½ to 1 oz. (15 to 30 mils).
2. Tinctura Cascarillæ.
   Dose, ½ to 1 dr. (2 to 4 mils).

Aurantii Cortex Recens.
Aurantii Cortex Siccatus.

PREPARATIONS

1. Tinctura Aurantii.
   Dose, ½ to 1 dr. (2 to 4 mils).
2. Vinum Aurantii.—Contains about 15 per cent. alcohol.
   Dose, ½ to 2 oz. (15 to 60 mils).
3. Syrupus Aromaticus.
   Dose, ½ to 1 dr.
4. Syrupus Aurantii.
   Dose, ½ to 1 dr. (2 to 4 mils).
5. Infusum Aurantii.
   Dose, ½ to 1 oz. (15 to 30 mils).
6. Infusum Aurantii Compositum.
   Dose, ½ to 1 oz. (15 to 30 mils).
7. Aqua Aurantii Floris.—Orange-flower Water. Dose, ½ to 1 oz.
8. Syrupus Aurantii Floris.
   Dose, ½ to 1 dr. (2 to 4 mils).

CHARCOAL

Charcoal, on account of its extremely porous nature, has the property of absorbing gases; it will, for example, take up about eighteen times its own volume of oxygen. It was at one time largely used in medicine with the idea that it might absorb the fermentative gases formed in the stomach; this supposition is not correct, as when moist it loses this property.

Some of the virtues of charcoal are due to its power of absorbing oxygen, which it condenses and gives off in a very active condition to certain substances. For example, sulphuretted hydrogen or decomposing organic matter is quickly oxidised and destroyed by this drug. Most, but not all, of this action is lost when the charcoal is moistened with water. Wet charcoal is still capable of oxidising certain organic substances in solution, and the water passed through an ordinary charcoal filter is found to have some of its organic impurities destroyed. This property is, however, but feeble, and is very soon lost. Charcoal is not an antiseptic or disinfectant, but it is a useful deodorant, and is sometimes used as an application to foul ulcers, which it renders clean and sweet.

This drug has obtained a considerable reputation in the treatment of dyspepsia, but its exact mode of action is uncertain. Wilde argues from the fact that organic matter may undergo decomposition either as a result of aërobic or anaërobic bacteria; the former process results in a more or less complete oxidation, the latter only serves to produce intermediate products, some offensive and some toxic. He suggests the possibility of the oxygen carried by the charcoal converting an anaërobic to an aërobic form of fermentation. In this way the toxins and offensive bodies produced by the anaërobic bacteria would be oxidised. The second possibility is that the charcoal acts purely physically by spreading

itself out on the surface of the mucous membrane and, like bismuth salts, aiding the removal of mucus.

Charcoal has also the property of adsorbing to itself ferments and certain toxins: these substances are thus prevented from being absorbed and are removed with the charcoal in the fæces. Kaolin (white China clay) has a similar action, and great benefit with lowered mortality has followed its employment in Asiatic cholera, a disease which, in man, is at first localised in the intestine.

Charcoal has the power of precipitating certain colouring matters and alkaloids from their solutions. Thus, it may be used to decolorise organic solutions such as tea, and it will precipitate strychnine and morphine from solution.

It is probable that a trace of the drug may be absorbed, since particles have been detected in the epithelial cells of the duodenum on microscopical examination. But such absorption is of little significance.

MATERIA MEDICA

Carbo Ligni. Dose, 60 to 120 grs. (4 to 8 grms.).

CHAPTER XVIII

THE ACTION OF DRUGS ON RESPIRATION

SAPONINS. IPECACUANHA. EMETICS. APOMORPHINE. OXYGEN. CARBONIC ACID. CARBONIC OXIDE

RESPIRATION can be modified in a great variety of ways; through its centre in the medulla, through the bronchioles, and through the secretion of the bronchiolar mucous membrane.

The centre can be affected in several ways. Any alteration in the composition of the air inhaled may alter the depth and frequency of the respirations, and we make use of this fact in certain pulmonary diseases by sending patients to high altitudes, to moist atmospheres, or to other places with suitable climatic conditions for their particular form of complaint. Secondly, the centre can be affected through the blood, and any cause which tends to diminish oxygenation will increase the respiratory movements. Hæmorrhage, or a deficiency of hæmoglobin brought about in any way, such, for example, as might occur from the exhibition of one of the drugs which induce methæmoglobin formation, will produce the same effect. Iron and other drugs which increase the amount of hæmoglobin or red blood-corpuscles in the body have an indirect effect on the centre. Thirdly, we may attack the centre directly by such drugs as strychnine, ammonia, atropine, or caffeine (Fig. 74). Any of these, by increasing the irritability of the centre, not only augment the depth and number of respirations but also facilitate the coughing reflex; so that a particle of phlegm, which may be insufficient to arouse coughing before a dose of strychnine, will act as an adequate stimulus after such a dose. Lastly, respiration can be affected reflexly. It is hardly necessary to give examples of this, for everyone is familiar with the inspiratory efforts which are induced by the application of cold water to the surface of the body. We employ such a reflex in "smelling salts" by sniffing ammonia, or by using a snuff containing veratrine or aconitine. In each of these cases there is excitation of the nerve-endings in the nose, which reflexly induces several changes, especially increased depth of respiration, coughing and sneezing (Fig. 75).

The drugs which depress the centre are the narcotics and hypnotics, such as chloral and opium.

Drugs are sometimes used to act on the bronchiolar muscle.

It is possible to constrict these muscles directly, the same as any other plain muscle, by such drugs as barium or veratrine; but a constriction is more readily obtained by exciting the vagal endings, such as may be done by pilocarpine, physostigmine, or digitalis. This constriction prevents the air from getting out of the lungs, whilst the powerful force of inspiration causes the chest to distend so that a condition of dyspnœa obtains in which the chest is expanded almost to the maximum, yet little air enters or leaves the lungs. Certain drugs are employed to relieve this spasm or, as

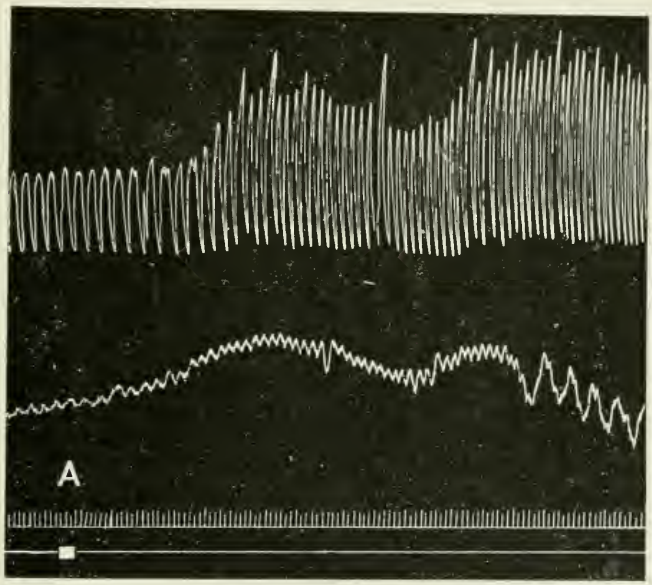


FIG. 74.—CAT. RESPIRATION AND B.P. RECORDS THE STIMULANT ACTION OF Am_2CO_3 ON THE MEDULLA.

The drug was administered at A by a vein. The respiratory effect is central, because it is still produced if the vagi are cut. The rise in blood-pressure is due to central vaso-constriction, since it is absent when the cord is severed high up. Respiratory upstroke = inspiration. Time = secs.

we call it, asthma. These usually act by depressing the vagal nerve-endings; they are atropine, hyoscyamine, hyoscine, lobeline, and nicotine: a few are effective by directly depressing the muscle, such as the nitrites, urethane, and the anæsthetics. The bronchioles may be constricted reflexly by exciting the nasal mucous membrane either electrically or by means of some drug, such as bromine or ammonia vapour.

The secretion from the bronchioles can be increased, first reflexly. Any drug which irritates the stomach induces an increased expectoration (Fig. 75). Thus we find that all the emetics are expectorants when given in small doses. The drugs which are used

to produce expectoration in this way are ipecacuanha, squills, ammonium, carbonate, saponins, tartar emetic, &c. These drugs need not be absorbed, and are certainly not excreted by the bronchiolar mucous membrane. Secondly, expectoration can be augmented by

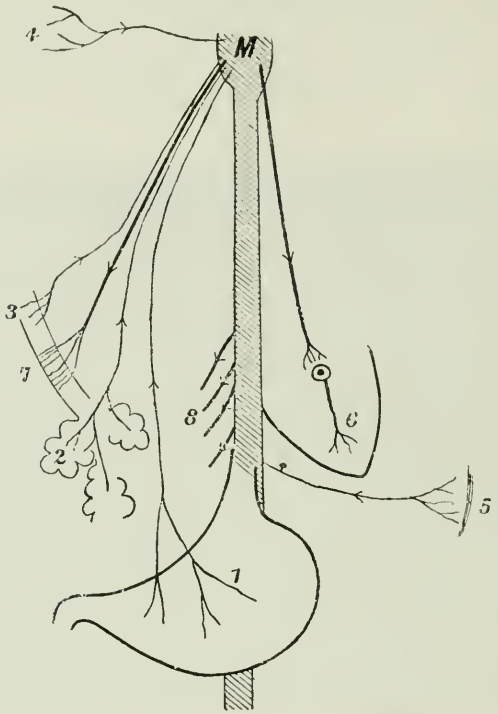


FIG. 75.—DIAGRAM TO SHOW THE ORIGIN OF CERTAIN REFLEXES.

M represents the medulla and spinal cord. 1 = sensory nerve-endings of the vagus in the stomach. 2 = sensory endings of the vagus in the lungs. 3 = sensory endings of the vagus in the bronchioles. 4 = sensory endings in the nose and mouth. 5 = afferent fibres from the skin. 6 = vagus nerve to the heart. 7 = motor nerve to the bronchioles. 8 = motor nerves to vessels, intestines and other plain muscle, and to voluntary muscle.

Stimulation of 1 *if mild* = an expectorant action—ammonium carbonate, ipecacuanha, senega.

Stimulation of 1 *if severe* = emesis—zinc sulphate, copper sulphate, tartar emetic, &c.

Stimulation of 2 *and* 3 = closure of the glottis, broncho-constriction, coughing and sneezing, cardiac inhibition—irritant vapours such as bromine or nitric acid.

Excitation of 4 = sneezing, coughing, bronchial asthma, slowing of respiration, cardiac inhibition, and possibly vomiting—snuffs, veratrine, aconitine, irritating vapours and powders.

Excitation of 5 *if mild* = stimulation of respiration, vaso-constriction, cardiac acceleration—mustard plasters, blisters, and other forms of counter-irritation.

Excitation of 5 *if severe* = depression of respiration, great vaso-dilatation and cardiac slowing—severe burns, surgical shock.

the excitation of the nerve-endings to the mucous glands by such drugs as pilocarpine. This method is not employed in practice on account of the increase of the other secretions, such as sweat and saliva. Thirdly, certain drugs are excreted by the bronchiolar mucous membrane, and act as expectorants during their excretion.

The drugs affecting secretion in this way are the alkalies, especially carbonates, potassium iodide, and the essential oils, those commonly employed being tolu, peru, turpentine, and camphor. The essential oils also act as antiseptics. The drugs which decrease expectoration are acids, belladonna, stramonium, and hyoscyamus.

To produce these various effects the drugs are sometimes inhaled. Thus, to relieve spasm of the bronchioles, stramonium, lobelia, chloroform, or amyl nitrite may be inhaled. Inhalations of creosote, benzoin, or carbolic acid are employed to disinfect foul secretions.

DRUGS OWING THEIR ACTION TO THE PRESENCE OF SAPONIN

Quillaia cortex, the bark of *Q. saponaria*. If it is macerated in water it froths, and hence it is termed soap-bark. The frothing is due to two toxic glucosides, quillaic acid and sapotoxin. Commercial saponin is composed of a mixture of these two substances together with the inert matter.

Senega root is obtained from *Polygala senega*. It contains two homologous glucosides, senegin and polygalic acid, which are identical with the saponins, sapotoxin and quillaic acid respectively.

The saponins are a group of glucosides possessing certain common properties, and are very widely distributed throughout the vegetable kingdom. The common characteristic of these bodies is that of forming a clear solution in water, which froths on shaking and forms emulsions with oils and resinous substances. Their chemical constitution is very uncertain, but they belong to a series having the formula $C_nH_{2n-8}O_{10}$, and on hydrolysis yield glucose and inactive substances to which the name sapogenin has been given. Possibly they have very large molecules and enter into colloidal solution: they dialyse with difficulty and can be salted out of their solutions like proteins. The different saponins vary considerably in their toxicity, the more powerful being spoken of as sapotoxins. The following is a list of the more important plants which contain active saponins:—

Saponaria officinalis, 4 *to* 5 *per cent. sapotoxin.*
Quillaia saponaria, 9 *per cent. sapotoxin.* } Most active.
Polygala senega.
Sarsaparilla (*smilax*) (not enough saponin to produce a therapeutic effect).
Agrostemma githago.
Digitalis purpurea (*digitonin*).
Claviceps purpurea (*ergotinic acid*).
Guaiacum.

The saponins from these plants vary much in toxicity: for example, the saponin from senega is only about one-eighth as

active as the sapotoxin from quillaia, and digitonin is much less active than either. They also vary in their rate of absorption; as a rule, very little saponin finds its way into the system from the alimentary canal, but that from Agrostemma is more rapidly absorbed than the other saponins.

The saponins are general protoplasmic poisons: they rapidly destroy amœbæ, cilia, intestinal worms, or undifferentiated protoplasm. A solution of 1 in 10,000 quillaia-sapotoxin kills the isolated gastrocnemius of the frog in three hours. If a saponin is added to freshly drawn blood, coagulation is retarded, the red blood-corpuscles are destroyed, and hæmoglobin is set free. Like all such irritant bodies, they contract the arterioles during direct perfusion and arrest the frog's heart in systole.

These drugs are strongly irritant, minute quantities being sufficient to produce inflammation of the nasal and conjunctival mucous membranes. They are irritant poisons when administered in sufficiently large doses by the mouth; and cause vomiting, diarrhœa, enteritis, and death from collapse. Saponins are not absorbed from the alimentary canal in appreciable quantity, so that, unless given in such large amounts as to give rise to local irritation, they produce no evil effects. They are used as expectorants to increase the flow of bronchial mucus, and it is said that they can maintain a gentle degree of expectoration over a prolonged period. This has been ascribed to the excretion of a minute amount of the drug by the bronchial mucous membrane, but is no doubt due to a reflex from irritation of the stomach, an effect obtained with all emetic substances.

The key to the understanding of all their toxic actions lies in their behaviour to cholesterins and lecithins, with which they combine in equimolecular amounts; the lipoids of the cells are thus changed physically and chemically and lose their functions. Thus the lipoid membrane of the red blood cells loses its power of retaining the viscous hæmoglobin which passes out of the stroma. Faust has succeeded in separating from cobra toxin an animal saponin—ophiotoxin, which behaves in many ways similar to the saponins.

If saponins are administered subcutaneously or intravenously they set up vomiting, diarrhœa, acute enteritis and nephritis, probably on account of their excretion by the gut and kidneys respectively. The *post-mortem* effects are indeed very similar to those seen after the injection of other irritant poisons such as cantharidin or podophyllotoxin. Saponins administered by the mouth are excreted by the rectum unchanged. They are but little used in medicine, but quillaia and senega are employed as expectorants. Saponins are used to emulsify oils, tars, and the like; they are added to various liquids such as ginger-beers to induce frothing, and are the active ingredient of the dry shampoo. Sarsaparilla and Hemidesmus should not find a place in the Pharmacopœia.

MATERIA MEDICA

Quillaiæ Cortex. PREP. Tinctura Quillaiæ. Dose, ½ to 1 dr. (2 to 4 mils).

Senegæ Radix. PREPS. 1. Infusum Senegæ. Dose, ½ to 1 oz. (15 to 30 mils). 2. Tinctura Senegæ. Dose, ½ to 1 dr. (2 to 4 mils).

IPECACUANHA

Ipecacuanha is the root from *Psychotria ipecacuanha*. It contains about 2 per cent. total alkaloid. Three different alkaloids are present: emetine, 72 per cent., cephæline, 26 per cent., and psychotrine, 2 per cent. Emetine is a quinoline derivative, and is methyl-cephæline, the relationship between emetine and cephæline being the same as that between codeine and morphine or caffeine and theobromine respectively. Ipecacuanha root also contains a saponin-like glucoside, and a second glucoside, ipecacuanhic acid. Commercial emetine is a mixture of emetine and cephæline.

ACTION

(1) *Small doses act as expectorants.*

(2) *Larger doses exert an irritant action to the whole of the gastro-intestinal canal, resulting in vomiting and diarrhœa.*

(3) *Depression of the central nervous system.*

The powdered root of ipecacuanha has an extremely irritant local action: minute quantities readily produce conjunctivitis and inflammation of the mucous membrane of the respiratory tract, with sneezing and coughing. Some people are peculiarly susceptible to its action, and in these the least trace applied to the nose causes violent coughing, a considerable flow of mucus, and in some cases an attack of spasmodic asthma, that is, a reflex bronchiolar constriction.

When taken by the mouth ipecacuanha has a bitter acrid taste and induces a considerable flow of saliva. On reaching the stomach it acts as an irritant: when the dose has been small it increases the secretion of gastric juice, but with larger amounts it quickly gives rise to a sensation of nausea which is more prolonged than that of apomorphine, followed by vomiting, during which the drug is usually voided and the action ceases. The ordinary accompaniments of vomiting are present; acceleration of the pulse, perspiration, and increased flow of mucus from the respiratory passages.

If ipecacuanha is injected subcutaneously, pain and inflammation, followed by suppuration and the formation of an abscess, are produced at the seat of inoculation, and symptoms of acute irritant poisoning rapidly develop, which are of a very similar character to those seen when arsenic, antimony, iron, or any of the more irritant of the vegetable purgatives are injected. There are nausea, vomiting,

and purging. The stools contain blood, and in the later stages of poisoning consist of little but blood-stained mucus: death follows from collapse. Œdema of the lungs is frequently seen as the result of hypersecretion of mucus.

The vomiting obtained with therapeutic doses of ipecacuanha is peripheral in origin, because the effect is produced as soon as the drug reaches the stomach, and in a quicker time and in smaller amounts than it can be produced by injection.

In lethal doses death is caused by collapse following the acute enteritis.

Ipecacuanha is a valuable expectorant in that the effect of one dose is prolonged over several hours, which is not the case with apomorphine.

The alkaloid emetine is largely employed in the treatment of amœbic dysentery, and whether given by the mouth or by injection acts as a specific in curing this disease. But emetine is not very toxic to amœbæ; quinine has a more powerful action, and methyl psychotrine, differing from emetine by two hydrogen atoms, is much more powerfully amœbicidal *in vitro* and much less poisonous than emetine to man. Yet neither quinine nor methyl-psychotrine cure dysentery. Therefore there must be other factors than amœba and emetine to consider. The importance of the host has been further demonstrated by the fact that emetine has no appreciable effect on the course of amœbic dysentery in the cat, while it cures the condition in man, and this even when the cat has been infected with human dysentery (*Entamœba histolytica*).

Carriers of amœbic dysentery cannot be treated successfully by emetine administered hypodermically, but they may be freed from infection by the administration of emetine bismuthous iodide, which, unlike emetine, may be given by the mouth.

It is easy for those suffering from this disease to establish some degree of tolerance to ipecacuanha. This is not, however, peculiar, as a similar tolerance may be obtained to many other irritant substances.

MATERIA MEDICA

Ipecacuanhæ Radix. Dose of powdered root, ½ to 2 grs. (3 to 12 ctgrms.) (expectorant), **15 to 30 grs.** (1 to 2 grms.) (emetic). Must contain not less than 2 per cent. of alkaloids.

Preparations

1. **Extractum Ipecacuanhæ Liquidum.** (2 per cent. alkaloids). **Dose, ½ to 2 m.** (3 to 12 centimils) (expectorant).
2. **Vinum Ipecacuanhæ.**—0.1 per cent. of total alkaloids. **Dose, 10 to 30 m.** (6 to 18 decimils) (expectorant). **4 to 6 grs.** (16 to 24 mils) (emetic).
3. **Pulvis Ipecacuanhæ Compositus.**—Dover's powder: ipecacuanha, 1; opium, 1; sulphate of potassium, 8. **Dose, 5 to 15 grs.** (3 to 10 dcgrms.).

4. **Pilula Ipecacuanhæ cum Scilla.**—Compound ipecacuanha powder, 3; squill, 1; ammoniacum, 1.
   Dose, 4 to 8 grs. (25 to 50 ctgms.).
5. **Trochiscus Ipecacuanhæ.**—$\frac{1}{4}$ gr. of ipecacuanha in each.
6. **Trochiscus Morphinæ et Ipecacuanhæ.**—Ipecacuanha, $\frac{1}{12}$ gr.; morphine hydrochloride, $\frac{1}{36}$ gr. in each.

EMETICS

The act of vomiting is brought about by a strong contraction of the abdominal muscles, which squeeze the stomach against an unyielding diaphragm at a period when the cardiac sphincter is relaxed and the pyloric closed. If the cardiac orifice remains closed during the spasm "retching" is the result.

There is a centre in the medulla which regulates the movements concerned in vomiting: it is closely associated with the respiratory centre, so that one can readily understand how small doses of drugs of this class may act as stimulants to the respiratory centre whilst larger amounts produce vomiting.

The centre can be excited by afferent impulses reaching it from many sources. A little veratrine sniffed up the nostrils irritates the peripheral terminations of the fifth cranial nerves and rapidly produces reflex coughing, sneezing, and sometimes even retching and vomiting. Tickling the soft palate with a feather is a common method of inducing emesis (reflex from the ninth cranial nerve). Likewise, certain central impressions, such as disgusting sights and smells, and any severe visceral pain, may lead to vomiting; but the commonest cause of emesis is irritation of the stomach or intestines.

Emetics have been divided into two groups—central emetics, those acting directly on the centre; and peripheral, those acting reflexly, generally by irritation of the stomach.

It is not always easy to decide whether a drug acts centrally or peripherally. The following are some of the methods employed in discriminating between these two classes:—

(1) Drugs which act purely on the centre will produce their effect much more rapidly when injected under the skin than when given by the mouth. It is stated that if the drug is injected directly into the circulation, and some time elapses before the vomiting occurs, the drug acts on the stomach; but if vomiting comes on immediately the action is on the medulla. Such reasoning is, however, fallacious, for if colchicine is given by the mouth vomiting is not induced nearly so rapidly as if it is injected into the circulation, and yet we know that colchicine acts on the peripheral vagal terminals in the stomach and intestines, and that its action, both as regards purgation and vomiting, may be eliminated by the use of atropine, which paralyses the same nerve-endings that colchicine

stimulates. If, however, vomiting is produced quicker when the drug is injected directly up one carotid into the brain than when injected into a vein, the evidence is distinctly in favour of a central effect.

(2) If relatively smaller doses are required by the stomach than by injection to induce vomiting, the inference is that the action is primarily on the stomach (ipecacuanha and tartar emetic).

(3) If the stomach is excised and replaced by a bladder of air, drugs acting centrally when injected into the circulation should induce the movements of vomiting as before. The converse is, however, not true, because vomiting may be produced by stimulating other afferent nerve-fibres than those from the stomach.

(4) Section of both vagus-nerves in the neck should be a valuable means of distinguishing between the two groups. If when the drug is given vomiting occurs as before section, the drug is probably central in action, and the converse should be true.

Vomiting may be divided into three stages. First, a feeling of nausea comes on, associated with glandular secretion from the mouth, larynx, bronchioles, and skin: during this stage the muscles are relaxed and the pulse and respiration rapid. This is followed by the stage of vomiting. The cardiac end of the stomach becomes relaxed and is filled from the contracted pylorus. Deep inspirations with a closed glottis are now made which induce a negative pressure in the chest, and this tends to draw up the stomach contents through the open cardiac orifice into the œsophagus. Strong contractions of the abdominal muscles, the diaphragm and stomach muscle, now occur simultaneously at a time when forced expirations are being made with a closed glottis. This produces the act of vomiting. The third stage is that of fatigue or even slight collapse in which the patient passes into a condition of languid ease or sleeps.

Classification of Emetics

Central	Peripheral
Apomorphine.	Sodium chloride.
	Zinc sulphate.
	Copper sulphate.
	Alum.
	Ipecacuanha.
	Ammonium carbonate.
	Mustard.
	Tartar emetic.
	Warm water.

These are the emetics in common use, but many drugs exert an emetic action in doses slightly in excess of therapeutic (vegetable purgatives). Drugs of the digitalis, pilocarpine, and veratrine

series, and the saponins in large doses, cause vomiting whether given by the mouth or injected subcutaneously, on account of the peripheral stimulation of the alimentary tract.

APOMORPHINE

Apomorphine hydrochloride is an artificial product, its formula representing that of morphine with the loss of one molecule of water. It is prepared by heating morphine or codeine hydrochloride with hydrochloric acid in a sealed tube at a temperature of 140 to 150° C. It is soluble in 50 parts of water, but solutions slowly decompose, so that when possible they should be prepared fresh.

Action

Excitation of the Central Nervous System, especially of the Vomiting Centre in the Medulla

In man the only marked effect of apomorphine, whether the drug be taken by the mouth or injected subcutaneously, is nausea and vomiting. These usually come on three or four minutes after injection, and are rarely delayed to fifteen minutes. After vomiting the nausea quickly passes off and no objectionable effects are observed. The vomiting is associated with the symptoms characteristic of nausea, namely, lassitude, weakness, salivation, perspiration, a flow of tears, and increased secretion of mucus from the glands of the nose, throat, and respiratory passages, together with acceleration of the heart and respiration; these associated effects are quite transient and cease with the vomiting.

The emesis is central; this can be shown by tying the vessels so that no drug can reach the stomach or intestines, when an injection of the drug still produces violent vomiting, whereas if the vessels are tied so that no drug reaches the medulla vomiting does not occur. Moreover, vomiting may be produced immediately, by painting the medulla with a solution of the drug. Apomorphine has considerable advantages over peripheral emetics in that it can be injected subcutaneously without giving rise to evil effects, and its action is very rapidly obtained.

Other Actions.—Apomorphine, when administered in large doses, stimulates the respiratory centre and respiration is quickened; this effect is in marked contrast to that of morphine, in which the respiratory centre is depressed.

Small doses of apomorphine (too small to induce nausea) increase the secretion of mucus from the respiratory tract and are thus *expectorant*, aiding in the removal of tough mucus by coughing. We have noted previously that an expectorant action is invariably obtained with small doses of emetics of every kind. This expectorant action with apomorphine is independent of local irritation. It seems to be impossible to excite the vomiting centre, whether

directly or reflexly, without stimulating respiration and the flow of bronchial mucus.

In very large doses there is some excitation of the higher centres in the brain. Thus dogs become very excited and restless, constantly moving round in a circle, and later may exhibit tetanic spasms. Eventually the excitement gives place to depression, reflexes are abolished, and coma gradually ensues, death resulting from respiratory failure.

In the frog the irritability of both striped and cardiac muscle is first diminished and finally abolished by the direct application of apomorphine; the same effect is not seen in mammals. This action on muscle, like the expectorant action, has been stated to be a constant effect, which can be obtained with all specific emetic substances (Harnack).

MATERIA MEDICA

Apomorphinæ Hydrochloridum. Dose, $\frac{1}{20}$ **to** $\frac{1}{10}$ **gr.** (3 to 6 mgrms.) hypodermically, $\frac{1}{10}$ **to** $\frac{1}{4}$ **gr.** (6 to 16 mgrms.) by the mouth.

Preparation

Injectio Apomorphinæ Hypodermica.—1 per cent. Must be freshly prepared.

Dose, 5 to 10 m. (3 to 6 decimils).

Tartar-Emetic

The direct emetics will be considered in their appropriate places, but a few words are necessary with regard to tartar-emetic, since it is believed by some writers to act on the medulla. Like salts of other heavy metals, in large doses it is irritant to the mucous membrane of the alimentary canal and sets up nausea and vomiting. When injected into the circulation the same effects are produced, but the dose must be larger, and the vomiting is not so prompt. These facts at once show that the action is mainly peripheral. Those who favour the central theory claim that vomiting movements are still obtained by antimony even when the stomach is replaced by a pig's bladder; but this is easily explained by irritation of some other part of the alimentary tract. Irritation of the intestine produces vomiting as readily as irritation of the stomach. Further, they assert that if the vagus-nerves are cut below the diaphragm, tartar-emetic only causes vomiting when injected and not when given by the mouth. This, however, supposing it to be correct, which is doubtful, does not prove a central action, because it is easy to conceive other reflex effects; for example, vomiting may result from stimulation of the vagal endings in the lungs.

It must also be remembered that, when the metal is given by the mouth, only the merest trace is absorbed, and, further, that

antimony has no known stimulant action on the medulla, as shown on the cardio-inhibitory, vaso-motor, or respiratory centres. We must, therefore, conclude that there is no evidence sufficiently satisfactory to place tartar-emetic amongst the central emetics.

ON CERTAIN GASES WHICH INFLUENCE RESPIRATION

OXYGEN

If a healthy person is allowed to inhale pure oxygen no effect can be observed, and it is quite impossible for the inhaler subjectively to discriminate it from air. It produces no increase in the respiratory exchange and no augmented oxidation of the tissues.

Oxyhæmoglobin is a definite chemical compound, and is practically saturated with oxygen during normal respiration, so that, as far as the hæmoglobin is concerned, no advantage is to be derived by increasing the partial pressure of oxygen in the inhaled air. An analysis of normal arterial blood shows the presence of about 18.5 per cent. by volume of oxygen as oxyhæmoglobin, and also about 0.6 per cent. of oxygen in simple solution in the blood plasma. Although a substitution of oxygen for air during inhalation cannot affect the oxyhæmoglobin to any extent, yet it increases the percentage of oxygen dissolved in the plasma, which may rise as high as 3 per cent. During normal oxidation of the tissues the oxygen in solution is first to go before the combined oxygen is called upon. Further, this combined oxygen is never entirely used up: in the normal cycle of the circulation not more than about 30 per cent. of it is used, and even in asphyxia the blood still contains some oxygen.

The inhalation of oxygen, whilst appearing to increase the amount of oxygen in the blood only slightly, yet does so very beneficially, since all the extra oxygen so absorbed is employed first by the tissues before the oxyhæmoglobin is called for.

Oxygen is essential for the proper working of isolated vascular tissues. For example, a strip of the heart-muscle from the turtle may be kept beating for seventy hours, that is, until dissolution begins, if only it is bathed in a suitable solution containing oxygen. The rabbit's heart can be kept for many hours in vigorous activity, provided it is perfused with an oxygenated Ringer's solution containing a trace of glucose: without the oxygen the beat rapidly becomes weak, but it is again augmented by running oxygen through the perfusing solution.

From these facts it is obvious that the inhalation of oxygen may be of great use in many conditions where the normal oxygenation is deficient. In cases of severe hemorrhage, or in which the hæmoglobin has been destroyed by nitrites, by CO (coal-gas), or by the benzene compounds, life can be prolonged by oxygen inhalation when under the ordinary condition of affairs death would

ensue from asphyxia. In various diseases of the lungs and heart associated with cyanosis, the inhalation of oxygen frequently causes the cyanosis to disappear, at least temporarily.

Oxygen is generally administered mixed with air, inhalations being given for a few minutes at a time at short intervals.

Carbonic Acid, CO_2.—Pure air should contain not more than about 0.03 per cent. of carbonic acid, but an excess of this amount, even up to 3 per cent., produces no poisonous symptoms. It is only when about 5 per cent. is present that dyspnœa becomes evident, and it is not till the percentage is still further increased, up to 10 per cent., that symptoms of narcosis develop. Carbonic acid, therefore, is not a toxic substance of importance.

Carbonic Oxide, CO.—Poisoning from this gas may occur, either from the absorption of coal-gas, which contains from 6 to 12 per cent. CO, or water-gas, which contains about 30 per cent. Carbonic oxide is also responsible for the deaths produced by the after-damp of mines. Carbonic oxide combines with hæmoglobin and forms a definite compound having a pink colour. The spectrum is shown in Fig. 69. It differs from oxyhæmoglobin in that it is not reduced by such bodies as ammonium sulphide.

The symptoms are such as may be observed as a result of deprivation from oxygen: they begin with dizziness and shortness of breath, especially marked on the least exertion, and are later followed by loss of consciousness. These are probably only due to lack of oxygen, since an animal placed in oxygen at two atmospheres pressure is not in any way injured by forcing in carbonic oxide. During recovery the gas is given off again by the lungs. Whenever an atmosphere contains anything above 0.15 per cent. CO it should be regarded as dangerous to life.

The affinity of CO for blood is about 200 times greater than that of oxygen. If 80 per cent. of the hæmoglobin of the body is converted to COHb death occurs, and 0.3 per cent. CO in air is sufficient to effect this in an hour. The inveterate inhaler of cigarette smoke always retains a considerable amount of CO, sometimes neutralising 10 per cent. of the available hæmoglobin.

CHAPTER XIX

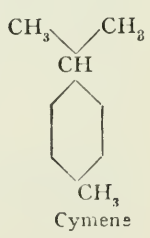
ESSENTIAL OILS

Most plants contain in their seeds, fruit, leaves, flowers, &c., volatile bodies which give rise to a characteristic odour and taste. These bodies have an oily consistency, but, unlike the fatty vegetable oils, such as olive or linseed oil, which consist of non-volatile glycerides, these oils are volatile and cannot be saponified; and the odorous constituents can generally be separated by distilling the macerated plant-part in a current of steam.

Volatile or essential oils are usually composed of a complex mixture of substances, but the characteristic property is due to one definite compound. Many of the essential oils, therefore, have common constituents, and yet differ in taste, smell, and other properties because of a small percentage of some highly odoriferous compound.

Ordinary turpentine is the best known of these bodies. It is obtained as an exudation by making shallow cuts into the stems of pine trees. The turpentine so obtained is distilled in a current of steam, a liquid "oil of turpentine" passes over in the distillate, and a resin is left. Turpentine is, therefore, an oleo-resin, that is, it consists of an essential oil containing a resin dissolved in it. Oil of turpentine, in common with most of the volatile oils, slowly oxidises in air, and is converted into *resin*.

The volatile oils are composed of bodies belonging to the aromatic or benzene series, and most of them contain one or more terpenes, which are volatile substances, having the formula $C_{10}H_{16}$, and which may be readily converted to cymene. All these terpenes are closely related to one another. The following are the more important:—



Cymene

Pinene ($C_{10}H_{16}$), a liquid occurring in all pine trees (turpentine) and in many other essential oils, such as oil of lemon, thyme, or parsley.

Camphene ($C_{10}H_{16}$), a solid terpene occurring in a large number of essential oils, such as oil of ginger and valerian. It is obtained also from camphor.

Limonene ($C_{10}H_{16}$), contained in oils of lemon, lavender, caraway, and turpentine.

Some volatile oils contain terpenes only, but many of them

have also oxidised benzenoid derivatives, phenols, ketones, acids, and other bodies. Some of these oxidised products crystallise out when the oil is sufficiently cooled, and they are then known as *stearoptenes*, of which menthol, camphor, and thymol are examples. Some resins form an emulsion when rubbed up with water; this is due to the presence of gum. Ammoniacum, galbanum, and myrrh are representatives of such *gum-resins*.

Balsams are essential oils containing resin and either cinnamic or benzoic acid: they may be solid or liquid. The oils extracted from some of the cruciferæ contain sulphur compounds, which give them a very disagreeable odour, such as allyl sulphide $(C_3H_5)_2S$ from oil of garlic. Oil of bitter almonds consists of benzaldehyde and oil of gaultheria of methyl salicylate; oil of mustard is liberated from a glucoside by decomposition. When obtained in a state of purity these oils are clear, colourless liquids, but assume a yellowish tint and an acid reaction on keeping, due to the formation of resin. They are almost insoluble in water, but can easily be dissolved in alcohol, ether, or chloroform.

Volatile oils, therefore, differ very considerably from one another, but they all possess two common characteristics, their volatility and the presence of the benzene nucleus. And it is principally to these two properties that they owe their use in medicine. Therefore, while in small doses their action is very similar, when large doses are administered and the specific effect of the drug after absorption comes into play, their action will be found to differ considerably.

For convenience of description, the volatile oils and their relatives the oleo-resins, resins, and balsams may be divided into the following groups, according to their use:—

I.—Turpentine Group

(a) Oils and Oleo-resins

Oleum terebinthinæ, obtained by steam distillation from the oleo-resin of *Pinus sylvestris*. The crude oleo-resin, that is, turpentine, contains about 15 per cent. oil of turpentine.

Terebenum is obtained by agitating oil of turpentine with sulphuric acid and then distilling in a current of steam. It is composed of a mixture of terpenes.

Oleum abietis, the oil distilled from the fresh leaves of *Abies sibirica*.

Terebinthina Canadensis (Canada balsam) is an oleo-resin containing 75 per cent. resin. It is not a true balsam since it contains no cinnamic or benzoic acid.

Terebene is a mixture of dipentene and other hydrocarbons.

(b) Resins

Resina, remaining after the oil of turpentine is distilled off from the crude oleo-resin (turpentine). The chief constituent is abietic acid, $C_{18}H_{27}COOH$.

Ammoniacum, a gum-resin obtained from the flowering stem of *Dorema ammoniacum*. Among other bodies it contains the complex $C_6H_4\begin{matrix}OH\\C_2H_5\end{matrix}$

Myrrha, a gum-resin exuded from the stem of *Balsamodendron myrrha*.

Guaiacum, the wood of *G. officinale*. The chief constituent is the *resin*, which is present to 20 per cent. in the heart-wood, and which exudes from the wood spontaneously in tears. Guaiacum also contains several saponins.

(c) Tars

Pix liquida (wood-tar) is obtained by destructive distillation of *Pinus sylvestris*. It is a very complex mixture, containing resin, charcoal, acetic acid, oil of turpentine, pyrocatechin, and phenol.

Formerly it was much used in skin diseases, but has now been replaced by naphthol, resorcinol, and other pure substances.

Pix carbonis præparata (coal-tar) is obtained by heating commercial coal-tar so as to drive off the ammonia it contains. Its antiseptic properties are due to phenol, naphthalene, and allied bodies.

Oleum cadinum, from destructive distillation of *Juniperus oxycedrus*. It is less viscid than ordinary tar.

Ichthyol, from the distillation of bituminous shale. It contains 10 per cent. sulp ofhur. It i sa mild antiseptic of doubtful value.

(d) Balsams, or oleo-resins, containing cinnamic  CH=CH.COOH and benzoic  COOH acids

Styrax præparatus (prepared storax), the purified balsam from the trunk of *Liquidambar orientalis*. Storax must yield not less than 20 per cent. of cinnamic acid. The volatile oil is never present to more than 1 per cent. It also contains styrene  $CH=CH_2$. It is quite efficacious in the treatment of scabies and pediculi.

Benzoinum, a balsamic resin exuding from artificial incisions of the bark of *Styrax benzoin*. It contains nearly 40 per cent. of cinnamic and benzoic acids. The percentage of volatile oil is small. It is used to prevent fat becoming rancid.

Balsamum Peruvianum, a resinous exudation from the bark of *Myroxylon perciræ*. It contains 30 per cent. of resin, 60 per cent. of volatile oil, and some benzoic acid. It is neither irritant to the skin, nor poisonous. It is used externally as a remedy in itch and internally to reduce bronchial secretion.

Balsamum Tolutanum, obtained by incisions into the stems of *Myroxylon toluifera*. It contains 12 to 15 per cent. of free cinnamic acid.

II.—Urinary Disinfectants or Diuretics

Copaiba, an oleo-resin from the trunk of *Copaifera langsdorfii*. It contains about 50 per cent. volatile oil (sesquiterpene), the rest being a mixture of acid resins.

Cubebæ fructus (cubebs), the dried unripe fruit of *Piper cubeba*. It contains 10 to 18 per cent. volatile oil (oleum cubebæ), besides terpenes, cubeb camphor—an oxidation product present in largest amount in old oils—and a bitter substance, cubebin, which is not absorbed.

Oleum santali, Santal-wood oil. Obtained by distillation from the wood of *Santalum album*. It contains two oxidised substances, santalol and santalal, which can be reduced to a sesquiterpene identical with that of copaiba. It is required to contain not less than 90 per cent. of alcohols calculated as santalol.

Oleum juniperi, obtained by distillation from unripe fruit of *Juniperus communis*: it generally contains about 1 per cent. volatile oil.

Buchu folia, obtained from *Barosma betulina*. They yield from 1 to 2 per cent. of volatile oil. A bitter principle is also present.

III.—Malodorous

Asafetida, a gum-resin obtained from *Ferula fetida*. It produces from 4 to 8 per cent. of a volatile oil, containing some oil of garlic $(C_3H_5)_2S$, 25 per cent. gum, and 50 to 70 per cent. resin.

Valerian, the root of *Valeriana officinalis*. Contains about 1 per cent. volatile oil, which has no odour when freshly distilled, but which, on exposure to air, soon develops a very unpleasant smell. The oil is composed of terpenes, Borneo-camphor, and fatty acids. The active constituents in oil of valerian exert mild depressant effects on the central nervous system. The galenical preparations are unstable and often inactive. Borneol isovalerate (Bornyval) and a mixture of menthol with the menthyl ester of valerianic acid (Validol) have been introduced as substitutes, but they too are unstable.

IV.—Carminatives and Flavouring Agents

The first five of these do not depend on the volatile oil for their active constituents.

Piper nigrum (black pepper).—Cardamom and nutmeg belong to this order, and, like ginger, contain a large percentage of manganese. The taste is the result of a resin and an alkaloid piperine.

Zingiber (ginger).—The scraped and dried rhizome. It contains from 2 to 3 per cent. of volatile oil, an oily substance, gingerol, and a resin.

Capsici fructus (cayenne pepper) is the dried fruit of *Capsicum minimum*. It contains about 0.02 per cent. capsaicin ($C_9H_{14}O_2$), which causes the characteristic pungency. It also contains a fixed oil, a volatile oil, and some resin.

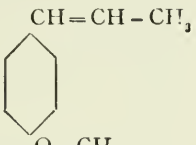
Pyrethri radix, obtained from *Anacyclus pyrethrum*. It contains an acrid resin, two acrid fixed oils, a little volatile oil, and some tannin.

Armoraciæ cortex (horse-radish) is the product of *Cochlearia armoracia*. Its principal constituents are sinigrin, myrosin, and about 0.05 per cent. volatile oil.

Coriandri fructus is the product of *Coriandrum sativum*. It contains about 1 per cent. of the official oil *Oleum coriandri*.

Cardamomi semina are from *Elettaria cardamomum*. They have nearly 5 per cent. of volatile oil and 10 per cent. of fixed oil.

Anisi fructus, the dried fruit of *Pimpinella anisum*. *Oleum anisi* is distilled from the fruit. It contains among other substances anethole—about 90 per cent.—



Anethole.

Fœniculi fructus, from *Fœniculum capillaceum*.

Anethi fructus (Dill fruit).—Dried ripe fruit of *Peucedanum graveolens*. *Oleum anethi* is a pale yellow oil distilled from the fruit.

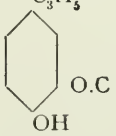
Carui fructus.—Caraway fruit is the product of *Carum carvi*. It contains from 3 to 7 per cent. of the volatile oil, *Oleum carui*.

Cinnamomi cortex.—Its chief constituents are the volatile oil *Oleum cinnamomi*, 0.5 to 1 per cent. (containing about 75 per cent. cinnamic aldehyde $C_6H_5.CH:CH.CHO$), and a little tannin.

Myristica.—Nutmeg is the dried seed. When distilled with water nutmegs yield from 8 to 15 per cent. *Oleum myristicæ*. It produces in cats well-marked fatty degeneration of the liver associated with jaundice and coma as in phosphorus poisoning.

Anthemidis flores (chamomile flowers) contain *Oleum anthemidis*, a bluish oil distilled from the flowers.

Caryophyllum.—The dried flower buds of *Eugenia caryophyllata*. It contains 15 to 20 per cent. *Oleum caryophylli* and about 12 per cent. of tannin. The oil is composed mainly of eugenol (not less than 85 per cent.).



Eugenol.

Aurantii cortex, recens, and siccatus.—Bitter orange peel contains besides the oil a bitter glucoside, aurantiamarin.

Limonis cortex, the fresh outer part of the fruit of *Citrus media*. It contains the official volatile oil *Oleum limonis*, and a bitter glucoside, hesperetin. The oil must contain not less than 4 per cent. of aldehydes calculated as citral.

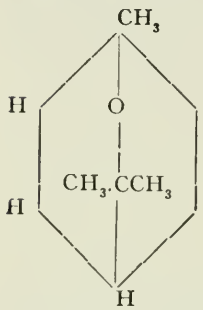
Rosæ Gallicæ petala.—The odour is due to the official oil *Oleum rosæ*.

Oleum cajuputi, obtained by distillation from leaves of *Melaleuca leucadendron*. It must contain not less than 45 per cent. eucalyptol.

Oleum rosmarini, by distillation of flowering tops of *Rosmarinus officinalis*. Must contain not less than 10 per cent. alcohols calculated as borneol.

Oleum lavandulæ, by distillation from the flowers.

Oleum eucalypti, obtained by distillation from the leaves of *Eucalyptus globulus*. 45 per cent. of the oil must be eucalyptol, a body which is also present in the oils of cajuput and lavender.



Eucalyptol or Cineol.

Oleum menthæ piperitæ, obtained by distillation from fresh flowering *mentha piperita*. It contains not less than 50 per cent. of menthol.

Oleum menthæ viridis, obtained by distillation from the fresh flowering *Mentha viridis*.

This list, however, does not include all official plants containing volatile oils, since some of the oils possess such special characteristics as to be more conveniently examined under another heading, such, for example, as mustard. Many plants contain, along with the volatile oil, other and more important substances, such as hydrocyanic acid in the case of bitter almonds, and filicic acid in male fern.

ACTION OF THE VOLATILE OILS IN GENERAL

External.—The volatile oils are used as antiseptics both externally and when taken by the mouth. This is a specific action on protoplasm, an effect which is characteristic of the benzene derivatives to which the terpenes belong: the effect is aided by the volatility of the oils, which are enabled the more easily to enter the cell and get into contact with the protoplasm. Volatile oils, in sufficient concentration, are rapidly germicidal to all forms of bacteria.

When applied to the skin they produce irritation, itching, and redness, followed by numbness, the irritant effect again being increased by the volatility of the drug. Oil of cloves is used in dentistry both to relieve pain and act as an antiseptic; and thymol was formerly employed in surgery, but it is now discarded on account of its insolubility.

The redness is the result of dilatation of the vessels, and the volatile oils are therefore rubefacient; arnica is used popularly for this purpose. Certain oils, such as oil of mustard, affect the skin in a specific manner; others, as menthol, cause a specific stimulation of those nerves conveying the sensation of cold. The oils of rosemary, juniper, and savin are the most irritant and are rarely taken internally.

Many of these drugs are used as inhalations to affect the *bronchioles* locally. The vapour of turpentine so administered arrests the secretion of mucus, and has therefore been employed in conditions in which there is profuse secretion and congestion. If air passed through oil of turpentine is blown on a portion of an animal's tracheal mucous membrane the secretion of mucus decreases and ultimately stops, whereas control experiments with air only rather tend to increase secretion. Others, such as eucalyptus, have been similarly used for phthisis and septic conditions of the lungs in which an antiseptic effect was desired; their employment for this purpose has been a disappointment.

Alimentary Canal.—The essential oils generally have an agreeable taste; they cause a hot sensation in the mouth, a reflex flow of saliva, and increased appetite. Many of them possess so powerful an odour that they are used in the form of smelling salts, to stimulate the medulla reflexly through the olfactory nerves.

In the stomach they exert much the same effect as on the skin, that is, they produce a mild form of irritation, leading to increased vascularity, more rapid absorption, and perhaps relaxation of the cardiac orifice; at the same time they exert their antiseptic action. These effects give rise to a feeling of warmth and well-being, and not infrequently to the eructation of gas and the relief of colic. Such bodies are generally spoken of as carminatives. Some of the good results obtained by volatile oils are no doubt suggestive, and arise from the pleasing sensations which they cause in the stomach. The influence of taste must not be forgotten: there is no doubt that a considerable increase of gastric juice will result reflexly from the stimulation of the taste nerve-endings, in much the same way as a pleasant odour may make one's mouth water; and it is also noticeable that the appetite is stimulated. Excessive doses give rise to gastro-enteritis, with vomiting and diarrhœa, the intestines being affected in much the same way as the stomach.

The essential oils are rapidly absorbed, they circulate unchanged in the blood, and can usually be detected in the breath. They may be administered with other substances to increase their rate of absorption, being in this respect like most other irritants and alcohol.

Blood.—The volatile oils when administered by the mouth produce a leucocytosis, especially of the polynuclear variety. As the effect is said not to occur when they are injected, it is

probably brought about by their irritant action on the alimentary canal.

Central Nervous System.—Only in very large—non-medicinal—doses do the volatile oils affect the central nervous system. The action consists of stimulation followed by depression, and is especially upon the brain. The effect is no doubt due to the benzene nucleus contained in the terpenes. Different oils vary considerably in the production of these effects: generally the stimulation is not a very marked feature; in the case of turpentine it is very transitory, and the ultimate narcotic effect is the more pronounced; in rabbits it is easy so to diminish the reflex excitability that poisonous doses of strychnine no longer cause convulsions. During the stimulation stage the blood-pressure rises and the depth and frequency of respiration are increased, the effects being due to excitation of the vaso-motor and respiratory centres respectively. With absinthe, and to a less extent with nutmeg, the reflex excitability can be so increased as to lead to convulsions of a reflex character and probably due to excitation of the cerebral cortex. (*See* Camphor.)

Fatty degeneration of various organs, such as the liver and kidney, has been described after the continuous administration of some of these oils.

Excretion.—The volatile oils are excreted by the lungs, skin, and kidneys. During excretion from the lungs their odour is readily recognised in the breath, and they exert a mild irritation leading to stimulation of the ciliated epithelium and to reflex coughing; they are used therefore as expectorants. Formerly it was hoped that they would exert a sufficiently strong antiseptic action in the lungs to arrest the growth of organisms, but this ideal has not been realised. Various preparations, such as oil of garlic, pitch, and others, are still used, however, in phthisis.

Some small amount is excreted by the skin and, acting as a mild stimulant, produces slight diaphoresis.

Volatile oil is excreted, combined with glycuronic acid, by the kidneys. It causes here, as elsewhere, a mild antiseptic and irritant action, the latter producing dilatation of renal vessels resulting in diuresis. This action is particularly well marked with the oils of copaiba and cubebs, but it can be observed with almost any of them. Many of the oils give a peculiar odour to the urine: oil of turpentine and oil of eucalyptol produce a sweetish odour somewhat resembling violets; this is probably not due to a new product, as most of the oil is excreted unchanged: the same odour can be obtained by agitating urine with turpentine.

Resins are excreted in the urine combined with glycuronic acid. The addition of acids to such a urine may result in a precipitate somewhat resembling albumen.

Special Uses of Certain Oils

The members of the **turpentine group** possess a more penetrating action on the skin than most other volatile oils. This is due to their greater volatility, the result of containing a large proportion of terpene. They generally have a nauseating taste, are more irritant to the alimentary canal than other oils, and are more likely to lead to lumbar pain, albuminuria, and hæmaturia during their excretion; for this reason they are seldom given internally.

They are used principally for their action on the skin, but oil of turpentine is sometimes employed as an anthelmintic for tape-worms.

The tars are used externally in the form of ointments for the purpose of stimulation in chronic cutaneous diseases. Resins have the general effects of the other volatile oils, common resin being generally employed as a mild stimulant to the skin. Ammoniacum, galbanum, and myrrh act like the volatile oils. Guaiacum has a nauseating taste and is rarely given: it is sometimes used empirically in syphilis, chronic rheumatism, and gout, but it is doubtful whether it has any action on these diseases other than subjective. Balsams are generally administered for their expectorant action; the cinnamic acid which they contain very slightly increases the number of polymorpho-nuclear leucocytes in the blood and the uric acid in the urine.

Urinary Disinfectant Group.—These drugs possess the ordinary properties of the other volatile oils, and are excreted like them mainly by the kidneys in combination with glycuronic acid, but a small percentage of oil is oxidised in the tissues. During their passage through the bladder and urethra they exert an antiseptic action, and urine which has been passed can be kept for days without undergoing putrefaction. They are, therefore, used in chronic inflammatory conditions of the bladder and urethra, especially gonorrhœa.

The acid resins which are present in the oils of copaiba and cubebs are also excreted by the kidneys, and give rise to considerable diuresis. When it is in large quantities the addition of concentrated nitric acid to the urine produces precipitation of this resin, which may be mistaken for albumen. The precipitate of resin, however, is soluble either in alcohol or excess of acid.

Glycuronic acid causes a reduction of Fehling's solution, but, unlike sugar, glycuronic acid is not fermented by yeast. Large doses of resin produce great irritation, as shown by pain in the loins, with blood and albumen in the urine.

Copaiba and cubebs are liable to produce erythematous or urticarial rashes as a result of irritation during excretion by the skin. Oil of Santal-wood is somewhat less irritant than copaiba, but otherwise its action is the same. Oil of juniper resembles oil of turpentine, but is not so irritating: it is employed as a diuretic.

Buchu is both diuretic and disinfectant to the genito-urinary tract.

The **malodorous** drugs possess the ordinary action of the volatile oils, but on account of their extremely nasty taste they are credited with beneficial subjective effects in certain functional disorders.

Carminative and Flavouring Agents.—These are in abundance in the Pharmacopœia. Some, as eucalyptus, have been largely used as antiseptics and disinfectants; others, as oil of cloves, in the relief of pain, such as neuralgia from a decayed tooth. Piper pyrethrum and capsicum are very irritant both to the skin and alimentary canal: their absorption in quantity may lead to inflammation of the kidneys.

Many are used either as flavouring agents or to give a pleasant odour to liniments: such are the oils of rosemary, lavender, rose and elder flowers, whilst the oils of cinnamon and lemon and the various preparations of orange are exhibited to conceal the taste of nasty medicine. The majority of the oils of this group are employed as carminatives, and are specially valuable in flatulence and abdominal distension in which there is no reason to fear gastro-intestinal irritation.

A word may be said here on the action of **musk**, the dried secretion from the preputial follicles of the musk deer. Though it does not contain an essential oil it appears to act like these bodies.

It is a stimulant to the medulla, and probably acts reflexly through the sensory nerves. It is used empirically in the treatment of hysteria and in various disorders supposed to be of spasmodic origin.

Trinitrobutyltoluol, $C_6H(NO_3)_3.CH_3.C_4H_7$, has the odour of musk, and is sold in perfumery under the name of artificial musk.

MATERIA MEDICA

Turpentine Group :—

Oleum Terebinthinæ Rectificatum. **Dose, 2 to 10 m.** (12 to 60 centimils), or **3 to 4 drs.** (12 to 15 mils) as an anthelmintic

PREPARATIONS

1. **Linimentum Terebinthinæ.**—With camphor and soft soap.
2. **Linimentum Terebinthinæ Aceticum.**—Glacial acetic acid and liniment of camphor.

Oleum Abietis.—Rubefacient like turpentine.

Terebinthina Canadensis.—Used for its adhesive properties.

Terebenum. **Dose, 5 to 15 m.** (3 to 10 decimils).

Resins :—**Resina.**—Used principally for adhesive plasters.

PREPARATIONS

1. **Emplastrum Resinæ** (adhesive plaster).—Resin, and lead plaster.
2. **Unguentum Resinæ.**

Ammoniacum. **Dose, 5 to 15 grs.** (3 to 10 degrms.).

PREPARATION

Mistura Ammoniaci. Dose, ½ to 1 oz. (15 to 30 mils). An emulsion of ammoniacum and tolu.

Myrrha. Dose, 5 to 15 grs. (3 to 10 decgrms.).

PREPARATION

Tinctura Myrrhæ. Dose, ½ to 1 dr. (2 to 4 mils).

Guaiaci Lignum.
Guaiaci Resina. Dose, 5 to 15 grs. (3 to 10 decgrms.).

PREPARATIONS

1. Mistura Guaiaci. Dose, ½ to 1 oz. (15 to 30 mils).
2. Tinctura Guaiaci Ammoniata. Dose, ½ to 1 dr. (2 to 4 mils).
3. Trochiscus Guaiaci Resinæ.—3 grs. in each.
4. Pilula Hydrargyri Subchloridi Composita.

Tars :—

Pix Liquida.—Used principally externally.

PREPARATION

Unguentum Picis Liquidæ.

Pix Carbonis Præparata.

PREPARATION

Liquor Picis Carbonis. — Contains saponin, which helps to suspend the tar when this preparation is prescribed with water (20 per cent.).

Oleum Cadinum.—Used externally.

Balsams :—

Styrax Præparatus.—A true balsam, used in making Tr. Benzoini Co.
Benzoinum. (*See* page 259.)
Balsamum Peruvianum. Dose, 5 to 15 m. (3 to 10 decimils).
Balsamum Tolutanum. Dose, 5 to 15 grs. (3 to 10 decgrms.).

PREPARATIONS

1. Syrupus Tolutanus. Dose, ½ to 1 dr. (2 to 4 mils).
2. Tinctura Tolutana. Dose, ½ to 1 dr. (2 to 4 mils). Balsam of tolu is precipitated by water.

Urinary Disinfectants :—

Copaiba. Dose, ½ to 1 dr. (2 to 4 mils).
Oleum Copaibæ. Dose, 5 to 20 m. (3 to 12 decimils).
Cubebæ Fructus. Dose, 30 to 60 grs. (2 to 4 grms.).

PREPARATION

Tinctura Cubebæ. Dose, ½ to 1 dr. (2 to 4 mils).

Oleum Cubebæ. Dose, 5 to 20 m. (3 to 12 decimils).
Oleum Santali. Dose, 5 to 30 m. (3 to 18 decimils).
Oleum Juniperi. Dose, ½ to 3 m. (3 to 18 centimils).

PREPARATION

Spiritus Juniperi.—10 per cent. oil of juniper. **Dose, 5 to 20 m.** (3 to 12 decimils).

Buchu Folia.

PREPARATIONS

1. Infusum Buchu. **Dose, 1 to 2 oz.** (30 to 60 mils).
2. Tinctura Buchu. **Dose, ½ to 1 dr.** (2 to 4 mils).

Malodorous :—

Asafetida. **Dose, 5 to 15 grs.** (3 to 10 decgrms.).

PREPARATIONS

1. Pilula Aloes et Asafetidæ.—Asafetida, aloes. Dose, 4 to 8 grs. (25 to 50 ctgrms.).
2. Spiritus Ammoniæ Fetidus.—Asafetida and ammonia. **Dose, 20** to 40 m. (12 to 25 decimils) for repeated, 60 to 90 (4 to 6 mils) for single administration.
3. Tinctura Asafetidæ. **Dose, ½ to 1 dr.** (2 to 4 mils).

Valerianæ Rhizoma.

PREPARATION

Tinctura Valerianæ Ammoniata. **Dose, ½ to 1 dr.** (2 to 4 mils).

Zinci Valerianas. **Dose, 1 to 3 grs.** (6 to 20 ctgrms.).

Carminatives and Flavouring Agents :—

Confectio Piperis.—Ward's paste. **Dose, 60 to 120 grs** (4 to 8 grms.).

Capsici Fructus. **Dose, ½ to 1 gr.** (3 to 6 ctgrms.).

PREPARATIONS

1. Tinctura Capsici. **Dose, 5 to 15 m.** (3 to 10 decimils).
2. Unguentum Capsici (Chili paste).

Zingiber. **Dose, 10 to 20 grs.** (6 to 12 decgrms.)

PREPARATIONS

1. Syrupus Zingiberis. **Dose, ½ to 1 dr.** (2 to 4 mils).
2. Tinctura Zingiberis. **Dose, 30 to 60 m.** (2 to 4 mils).

Pyrethri Radix.

PREPARATION

Tinctura Pyrethri.—Used locally as a sialagogue.

Armoraciæ Radix. **Dose, ½ to 2 drs.**

PREPARATION

Spiritus Armoraciæ Compositus. **Dose, 1 to 2 drs.** (4 to 8 mils).

Coriandri Fructus.
Oleum Coriandri. **Dose, ½ to 3 m.** (3 to 18 centimils).
Cardamomi Semina.

PREPARATION

Tinctura Cardamomi Composita. Dose, ½ to 1 dr. (2 to 4 mils).

Anisi Fructus.

PREPARATIONS

1. Aqua Anisi.—1 in 10. Dose, 1 to 2 oz. or more.
2. Oleum Anisi. Dose, ½ to 3 m. (3 to 18 céntimils).
3. Spiritus Anisi. Dose, 5 to 20 m. (3 to 12 decimils).

Fœniculi Fructus.

PREPARATION

Aqua Fœniculi.—1 in 10. Dose, 1 to 2 oz.

Anethi Fructus.

PREPARATIONS

1. Aqua Anethi.—1 in 10. Dose, 1 to 2 oz.
2. Oleum Anethi. Dose, ½ to 3 m. (3 to 18 centimils).

Carui Fructus.

PREPARATIONS

1. Aqua Carui.—1 in 10.
2. Oleum Carui. Dose, ½ to 3 m. (3 to 18 centimils).

Cinnamomi Cortex. Dose, 10 to 20 grs.

PREPARATIONS

1. Aqua Cinnamomi—1 in 10. Dose, 1 to 2 oz.
2. Pulvis Cinnamomi Compositus. Dose, 10 to 60 grs. (6 to 40 dcgrms.).
3. Tinctura Cinnamomi. Dose, ½ to 1 dr. (2 to 4 mils).
4. Oleum Cinnamomi. Dose, ½ to 3 m. (3 to 18 centimils).
5. Spiritus Cinnamomi.—1 in 10. Dose, 5 to 20 m. (3 to 12 decimils).

Myristica.

1. Oleum Myristicæ. Dose, ½ to 3 m. (3 to 18 centimils).
2. Spiritus Myristicæ. Dose, 5 to 20 m. (3 to 12 decimils).

Anthemidis Flores.

Oleum Anthemidis. Dose, ½ to 3 m. (3 to 18 centimils).

Caryophyllum.

PREPARATIONS

1. Infusum Caryophylli. Dose, ½ to 1 oz. (15 to 30 mils).
2. Oleum Caryophylli. Dose, ½ to 3 m. (3 to 18 centimils).

Aurantii Cortex. (*See under* Bitters.)

Limonis Cortex.

PREPARATIONS

1. Tinctura Limonis. Dose, ½ to 1 dr. (2 to 4 mils).
2. Oleum Limonis. Dose, ½ to 3 m. (3 to 18 centimils).
3. Succus Limonis. Dose, ½ to 4 oz. Contains 8 per cent. citric acid.
4. Syrupus Limonis. Dose, ½ to 1 dr. (2 to 4 mils).

Rosæ Gallicæ Petala.

PREPARATIONS

1. Confectio Rosæ Gallicæ.—Used as an excipient for pill masses.
2. Infusum Rosæ Acidum. Dose, ½ to 1 oz. (15 to 30 mils).
3. Syrupus Rosæ. Dose, ½ to 1 dr. (2 to 4 mils).

Oleum Rosæ.

PREPARATIONS

1. Aqua Rosæ. Dose, 1 to 2 oz.
2. Unguentum Aquæ Rosæ.—Cold cream, contains beeswax, almond oil, and borax.

Oleum Cajuputi. Dose, ½ to 3 m. (3 to 18 centimils).

PREPARATION

Spiritus Cajuputi.—1 in 10. Dose, 5 to 20 m. (3 to 12 decimils).

Oleum Rosmarini. Dose, ½ to 3 m. (3 to 18 centimils).

PREPARATION

Spiritus Rosmarini.—1 in 10. Dose, 5 to 20 m. (3 to 12 decimils).

Oleum Rosmarini.—Dose, ½ to 3 m. (3 to 18 centimils).

PREPARATION

Spiritus Rosmarini.—Used externally as a rubefacient.

Oleum Lavandulæ. Dose, ½ to 3 m. (3 to 18 centimils).

PREPARATIONS

1. Spiritus Lavandulæ. Dose, 5 to 20 m. (3 to 12 decimils).
2. Tinctura Lavandulæ Composita.—Oils of lavender and rosemary, cinnamon, nutmeg and red sanders-wood.
   Dose, ½ to 1 dr. (2 to 4 mils).

Oleum Eucalypti. Dose, ½ to 3 m. (3 to 18 centimils).

PREPARATION

Unguentum Eucalypti.—1 in 10.

Oleum Menthæ Piperitæ. Dose, ½ to 3 m. (3 to 18 centimils).

PREPARATIONS

1. Aqua Menthæ Piperitæ. Dose, 1 to 2 oz.
2. Spiritus Menthæ Piperitæ. Dose, 5 to 20 m. (3 to 12 decimils).

Oleum Menthæ Viridis. Dose, ½ to 3 m. (3 to 18 centimils).

PREPARATION

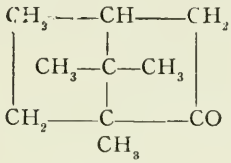
Aqua Menthæ Viridis. Dose, 1 to 2 oz.

STEAROPTENES

Camphor, Menthol, Borneol, Thymol

Stearoptenes are crystalline substances which are deposited when certain essential oils are allowed to stand. Their action in general resembles that of essential oils.

Camphor is obtained from the volatile oil of *Cinnamomum*



Camphor.

camphora. It may also be prepared artificially by oxidising camphene, a solid terpene $C_{10}H_{16}$. It is soluble in 1000 parts of cold water or in one part of alcohol. It is also readily soluble in oils, such as almond or olive. Milk also dissolves it easily, one ounce taking up nearly one drachm.

Two stereo-isomers of camphor exist: both varieties excite the cerebral cortex, the dextro or ordinary camphor of commerce being somewhat the more powerful.

Externally camphor has a mild antiseptic action, and is commonly used to keep away insects; it induces in them a state of lethargy, paralysis, and ultimately death. Camphor vapour paralyses undifferentiated protoplasm, white blood-cells become round and immobile, and the movements of cilia are either hindered or cease entirely. When it is rubbed into the skin it acts as an irritant and dilates the vessels, and so is used largely as a rubefacient.

Digestive System.—When taken by the mouth the effects of camphor closely resemble those of the volatile oils. It has a hot bitter taste, and induces a feeling of warmth and comfort in the stomach; it is therefore employed as a carminative. Large amounts, 30 to 40 grs., induce nausea and vomiting. Camphor is rapidly absorbed both from the skin and alimentary canal.

Central Nervous System.—This drug has a decided stimulant action on the cerebral cortex, and is in this respect like certain of the volatile oils, especially absinthe. If administered to animals with poorly developed cerebral hemispheres, it gives rise to descending paralysis of the central nervous system; this is characterised first by lethargy, due to implication of the cerebrum, then incoordination, pointing to an affection of the optic lobes and cerebellum, followed by cessation of respiration and medullary paralysis. Later, spinal reflexes disappear, and, last, the excitability of the motor nerves. Other drugs which similarly stimulate the cerebral cortex

and produce convulsions in mammalia, such as cocaine, also give rise to their secondary effect or general paralysis in the frog. If a rabbit is injected with paraldehyde or chloral till its reflexes disappear, these may return after a suitable injection of camphor. Camphor also mildly excites the medulla and so stimulates the respiratory centre and vaso-motor centre. The sweating which so often follows the administration of camphor may be due to the dilatation of skin-vessels.

The administration of large doses, say 40 grs., to man produces mental excitement, headache, confusion of ideas, giddiness, and inco-ordination of movement, followed by tremors and sometimes epileptiform clonic convulsions.

These convulsions are easily obtained in cats, dogs, and rabbits; they cease on the administration of chloroform, and do not occur if the camphor is injected after the removal of the cerebral cortex or if the cord has been previously severed. The stimulation gives place to depression, as shown by the ultimate stupor and loss of consciousness. In mammalia, death always results before the cord or motor nerve-endings are affected.

In small doses, 5 to 10 grs., camphor produces a sense of comfort, exhilaration, and stimulation of the mental faculties; the effect on some people is described as being very similar to that of alcohol.

Circulation.—Small doses of camphor, about 5 grs., dilate the skin-vessels and give rise to a feeling of warmth as with alcohol. This dilatation affects mainly the blush-area (compare nitrites) and is accompanied by sweating. Perfusion of camphor through isolated organs also shows dilatation, as indicated by the increased flow from the vein; but this is relatively small, for when small injections of the drug are made into a healthy animal's vein the blood-pressure does not fall.

In small doses camphor has little or no effect on the mammalian heart. In large doses the heart is slowed and the blood-pressure falls; the slowing is caused by a direct action on cardiac muscle, and the fall of blood-pressure is mainly vaso-motor in origin. Ten grains of camphor administered to man produces a slightly slower and a fuller pulse. It is often stated, mainly as the result of experiments on the frog's heart, that camphor excites the automatic centres in the heart. If the heart of the frog is brought to diastolic standstill by either muscarine or chloral hydrate the application of camphor may bring back the beat again, though in a very feeble and ineffective manner. In Germany this drug is largely used to revive the circulation in dying patients in whom the automatic centres of the heart are believed to be failing. Reliable clinical evidence of this action is lacking.

[1]Of course, during a convulsion the blood-pressure will rise in the same way as with strychnine (Fig. 32).

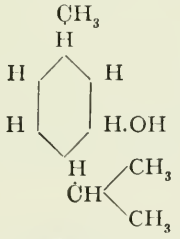
The dilatation of vessels will result in an increased loss of heat, and so the temperature is slightly lowered. Like the volatile oils

camphor is said to increase the leucocytes in the circulation. Respiration is little affected.

Absorption and Excretion.—Camphor is absorbed probably as such, but the rate of absorption is very irregular, and animals, after having a single dose, sometimes remain narcotised two or three days. In the tissues camphor is partly oxidised to camphorol, $C_{10}H_{16}O_2$: it is excreted in the urine combined with glycuronic acid, $(CHOH)_4.CHO.COOH$, as crystalline campho-glycuronic acid, together with an amido-derivative of the same acid. Campho-glycuronic acid is inactive, whilst camphoral has the same action as camphor, so that if this combination occurs rapidly, the effects of camphor quickly pass off, as in the dog. A small amount of the drug is also excreted from the skin and bronchioles.

Camphoric Acid, $C_8H_{14}(COOH)_2$, is an oxidation product of camphor. It is not very toxic, and may be administered in very large doses without serious effects. It is said to paralyse the nerve-endings going to sweat-glands like atropine, and is used clinically to prevent excessive sweating.

Menthol is the stearoptene from oil of peppermint, $C_{10}H_{19}OH$. It has much the same action as camphor, but is employed almost



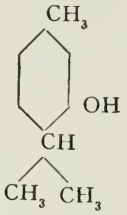
Menthol.

entirely for external use either in the form of an alcoholic solution or moulded into sticks. If it is rubbed on the skin a distinct sensation of cold is experienced, although, like camphor, the vessels are dilated and the skin temperature is higher. This sensation is followed by numbness and partial anæsthesia, and thus it relieves neuralgia when painted over the course of the painful spots. Apparently menthol has some specific action on certain nerves; it first excites those conveying the sensation of cold, and later penetrates the skin and paralyses the terminations of the ordinary sensory nerve-endings.

The other effects of menthol closely resemble those of camphor; thus it is carminative, but more liable than camphor to upset digestion. Absorption is very slow, and convulsions are not produced. Menthol is much more strongly antiseptic than camphor; it is excreted in the urine as mentho-glycuronic acid, which it renders aseptic, and to which it gives a sweet smell.

Borneol, $C_{10}H_{18}O$, has much the same action as laurel camphor.

Thymol is obtained from the volatile oils of *Thymus vulgaris* and *Carum copticum*. It is methyl-isopropyl-phenol, $C_6H_3.C_3H_7.CH_3.OH$, and its action closely resembles that of carbolic acid.



Thymol.

Thymol was introduced into surgery as a substitute for carbolic acid, but it is little used now on account of its sparing solubility, only 1 part dissolving in 1500 parts of water. Like carbolic acid, it penetrates the skin and produces local anæsthesia, but has the advantage of being much less irritant and a stronger antiseptic; a solution of 1 in 1000 with a small amount of alcohol is the usual strength employed. Thymol is occasionally used as a parasiticide; for example, in ringworm a 5 or 10 per cent. solution in alcohol is beneficial.

Internally thymol is irritant to the alimentary canal; a part is absorbed, and this is excreted in the urine in combination with sulphuric and glycuronic acids, but a body is also excreted which becomes green on exposure to air, and the urine of patients taking thymol is, therefore, often greenish in tint (thymol hydroquinone). It is given internally in 30-gr. doses as an anthelmintic to kill the Anchylostoma duodenale.

MATERIA MEDICA

Camphora. Dose, 2 to 5 grs. (12 to 30 ctgrms.).

Preparations

1. **Aqua Camphoræ.**—Contains about ½ gr. to 1 oz.
   Dose, 1 to 2 oz.
2. **Spiritus Camphoræ.**—1 in 10.
   Dose, 5 to 20 m. (3 to 12 decimils). Water precipitates the camphor.
3. **Linimentum Camphoræ.**—1 in 5 of olive oil (camphorated oil).
4. **Linimentum Camphoræ Ammoniatum.**
5. **Tinctura Camphoræ Composita.** *See* Opium.

Thymol.—$C_6H_3.OH.CH_3.C_3H_7$. Dose, ½ to 2 grs. (3 to 12 ctgrms.) as a pill.

Menthol.—$C_6H_9OH.CH_3.C_3H_7$. Dose, ½ to 2 grs. (3 to 12 ctgrms).

Preparation

Emplastrum Menthol. (Local anodyne.)

Borneol. (Not official.) Resembles camphor.

REMEDIES ACTING ON THE SURFACE OF THE BODY

Drugs are applied directly to the surface of the body, not only in lesions of the skin but also in various painful and deep-seated affections. In skin diseases where mild stimulation is required simple irritants may be employed, such, for example, as the volatile oils, resins, and tars. If astringents are desirable zinc oxide can be used, or, if there is hypertrophy of the stratum corneum, alkalies, sulphides, or salicylic acid may be indicated to dissolve it. On the other hand, when there is acute inflammation cooling or protective lotions would be indicated, such as spirit or lead.

Irritant drugs are used on the healthy skin with the object of relieving pain, diminishing congestion, and accelerating the absorption of inflammatory products in some distal part. Such irritant drugs may be said to act in three stages: when redness of the skin is the cardinal sign they are spoken of as *rubefacient*, and the skin presents the four classical signs of inflammation; it is hot, red, swollen, and tender. The tenderness is the result of excitation of sensory nerve-fibrils due to twisting, and the other symptoms are due to vaso-dilatation: the latter is probably not a direct effect of the drug on the vessel-walls, because irritants of this nature, applied in a soluble form directly to vessels, induce an opposite effect, that is, vaso-constriction.

When the irritant effect is more intense fluid exudes from the dilated vessels, it pushes off the outer from the living layer of cells, and collects to form a blister—the fluid of the blister commonly containing some of the irritant drug: drugs which do this are called *vesicants*.

A third class of skin irritants are the *pustulants*: these especially attack the skin-glands, and produce so intense an inflammation that small abscesses are formed round the hair follicles, and if the application is still continued these suppurating points may coalesce and produce a big abscess. These drugs have little effect on the dead epidermis, but when they come in contact with living cells, as those of the glands, they are extremely toxic. It is possible that in some cases the acid reaction of putrefying sweat may render the drug active, and so account for its selective effect on the glands.

The Mode of Action of Counter-irritants.—Irritants applied to the skin may be described as having three actions: a general, a local, and a special reflex action on the viscus related through the same spinal segment to the affected skin-area.

General Action.—Moderate stimulation of most sensory nerves causes (1) constriction of blood-vessels, especially those of the splanchnic area, with a resulting rise in blood-pressure; (2) acceleration of the heart; (3) transient stimulation of respiration and an insignificant rise in temperature. Effects of this kind can be shown to occur by irritating the skin of animals. Thus, if a leg of a

decerebrate cat is immersed in hot water, or if the flesh of the abdomen is burned with a searing iron, these effects are produced (Fig. 76). They are all reflex through the medulla, and no doubt like other reflexes serve a protective function, possibly in part by stimulating perception and volition to the needs of the occasion by increasing the amount of blood in the brain. The vascular volume of the brain always varies directly with the blood-pressure, since the vessels of this organ contain, for practical purposes, no vaso-motor nerves. The net result of this action is an alteration in the distribution of the blood. The abdominal organs contain

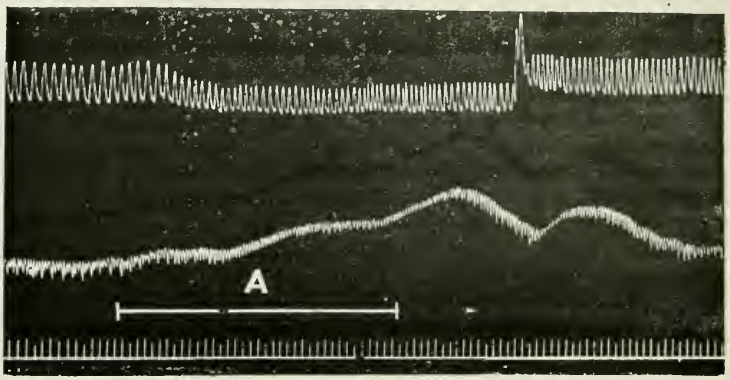


FIG. 76.—CAT. DECEREBRATE. SHOWING SOME OF THE GENERAL EFFECTS RESULTING FROM COUNTER-IRRITATION.

Upper curve = respiration Lower curve = blood-pressure. During A one hind limb was placed in hot water. Respiration became quicker, the heart-beat more rapid, and the blood-pressure rose mainly from vaso-constriction. Time = secs.

less, whilst the muscles of the body generally, the lungs, and the brain contain more.

When the stimulation is very intense, and especially when it is visceral, there is a fall of blood-pressure and reflex inhibition of the heart. The vaso-dilatation in the splanchnic area is enormous, and practically all the blood collects in the animal's veins. It is in all probability a vaso-motor paralysis of this nature which we term "surgical shock." Such shock may be induced in the frog by a sharp tap on the abdomen, when the heart stops, and there is a great dilatation of the splanchnic vessels.

Moderate skin irritation slightly increases metabolism; the absorption of oxygen, carbonic acid output, and nitrogenous excretion are all augmented, but the last only slightly. Blisters increase the number of the polynuclear white blood-corpuscles in the vessels. Probably these effects may also be ascribed to the altered distribution of the blood in the body.

Local effects have already been described, but it should be noted that the local dilatation of vessels in itself may sometimes give

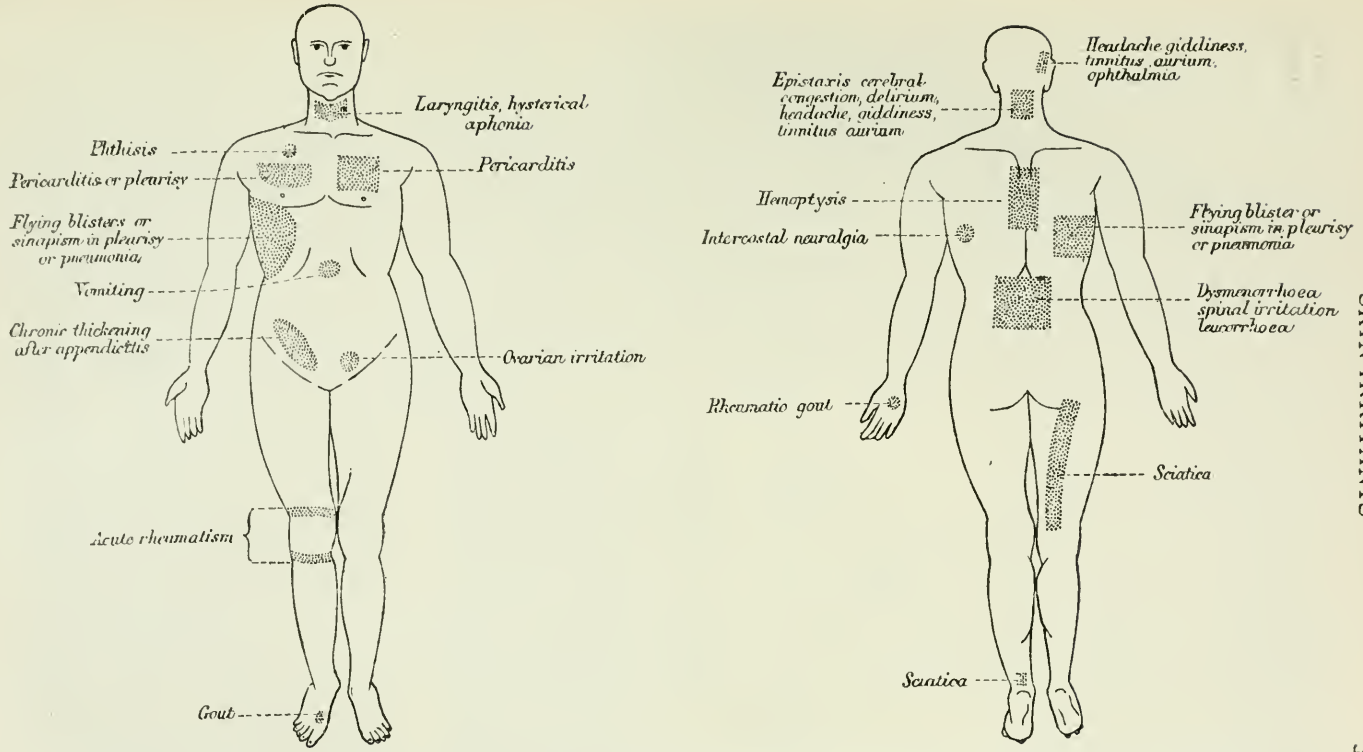


FIG. 77.—DIAGRAMS TO SHOW THE POINTS OF APPLICATION OF BLISTERS OR SINAPISMS IN VARIOUS DISEASES (BRUNTON).

relief from pain. For example, the application of a poultice to a suppurating sore will do this by diminishing the resistance to the flow of blood in the affected part.

The local inflammatory signs produced by any irritant application to the skin are axon reflexes: *i.e.* the stimulation of the sensory terminals in the skin causes a local reflex vaso-dilatation without the impulses passing through a nerve-cell. Inflammation of the skin can still be obtained after the nerve to the part has been cut, but not after it has been allowed to degenerate.

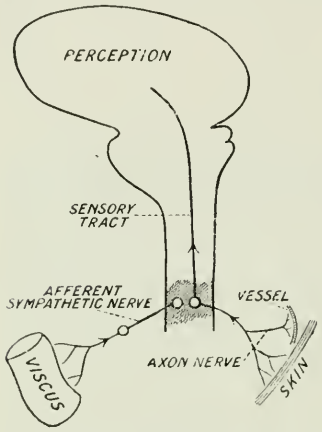


FIG. 78.—DIAGRAM TO EXPLAIN REFERRED PAIN AND COUNTER-IRRITATION (MACKENZIE)

If a sufficiently powerful impulse is started in a viscus it is supposed that in the cord it affects the nerve-cells in close proximity. If it spreads to a sensory cell, pain is perceived, but is referred to the peripheral distribution of the sensory nerve in the skin. The sensory nerve can thus be affected from two sources, visceral and cutaneous. If an irritant be applied to the skin where pain is *felt* in a visceral disease, the irritant may relieve pain by taking possession of the sensory nerve, which is then not so easily affected by stimuli from viscera. This diagram also shows how irritants to the skin cause local vaso-dilatation by an axon reflex.

Special Reflex Action. — All clinicians are agreed that counter-irritation is beneficial in certain pathological conditions, but that to produce the optimum effect the irritant must be placed in a definite and fixed position. Now if the benefit is the result of a general effect, there is no reason why the irritant should be placed at one spot more than at another, yet experience has shown otherwise: to give one example, to relieve the pain of trigeminal neuralgia the blister must be placed behind the ear.

It is well known that the viscera receive their sensory fibres from the same segments of the spinal cord as those from which the somatic sensory nerves arise. Head showed that visceral disease produced an exaggeration of the sense of pain in a definite fixed area, or areas in the skin, which he was able clearly to map out. These tender areas (Head's areas) do not correspond to the distribution of the posterior nerve-roots, but to the distribution of segments of the cord. Several of these areas, which he found to be affected by disease of internal organs, are the same as those which clinical experience has shown to be the best points for counter-irritation to affect those organs. It would seem, therefore, that there is an intimate relation between the central connexions of the sensory nerves of the viscera and the nerves which supply the sensation of pain and temperature, and which exert a trophic influence on the skin (Fig. 77).

It is probable that the trophic nerves to the viscera are in close association with the trophic nerves in the specially affected skin-

area. We know that visceral disease induces trophic changes in definite parts of the skin; it is fair to imagine that lesions of some special skin-area will affect the viscus segmentally related to it more than the rest of the body—and so we have an explanation of the phenomenon of counter-irritation.

Any stimulation of a sensory nerve from its periphery to its termination in the brain causes pain which is referred to the peripheral distribution of that nerve: it is well known that the man whose leg has been recently amputated still associates sensations with his toes. Afferent impulses normally pass from viscera to cord without sensation; but if the visceral stimulus is excessive the impulses may spread in the cord to the neighbouring cells, which may be thus excited and induce muscular contraction or pain. (Fig. 78.)

Severe cutaneous irritation is said to lead to pathological changes in the cells of the solar plexus.

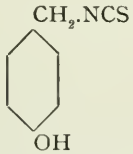
Drugs used for their irritant action on the skin may be divided into three groups:—

(1) **The Volatile Oils, Resins, and Balsams.**—Of these turpentine, terebene, and pine oils are especially used since they are more volatile, and therefore have a greater penetrating action than the other oils, and because their odour is pleasant. They are not very irritant, and are only used as rubefacients; but after very prolonged application blisters may be produced which, on account of the penetrating power of turpentine, are extremely painful and heal slowly.

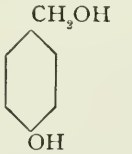
(2) **The Mustard Group.**—*Sinapis albæ semina* (white mustard seeds). They contain mucilage, about 25 per cent. of a fixed oil, a glucoside sinalbin, and an enzyme myrosin. In the presence of water the glucoside is hydrolysed by the myrosin.

$$C_{30}H_{42}N_2S_2O_{15} + H_2O = C_7H_7ONCS + C_6H_{12}O_6 + C_{16}H_{24}NO_5HSO_4$$

Sinalbin (inactive). Water. Acrinyl isothiocyanate, or oil of mustard (active). Dextrose. Sinapin acid sulphate.



Oil of mustard



Hydroxy-benzyl alcohol.

Sinalbin contains the complex hydroxy-benzyl alcohol.

Sinapis nigræ semina contain less mucilage, but over 30 per cent of fixed oil, a crystalline glucoside sinigrin, and myrosin. Hydrolysis of the glucoside in the presence of water is produced as before.

$$C_{10}H_{16}NS_2KO_9 + H_2O = CSNC_3H_5 + C_6H_{12}O_6 + KHSO_4$$

Sinigrin (inactive). Water. Allyl isothiocyanate (active). Dextrose. Potassium hydrogen sulphate.

Oleum sinapis volatile is obtained by distillation from dried ripe black mustard seeds. It must contain at least 92 per cent. of allyl isothio-cyanate.

Action

Mustard oil differs from the other volatile oils principally in that it is much more irritant; it is the best counter-irritant for general purposes, differing from cantharidin in the greater rapidity and pain attending its action. For local applications the mustard must be made up with cold water to a soft uniform cream and spread on muslin, cambric, or newspaper, the peripheral parts being folded over; this should be applied directly to the skin. The sinapism must be kept in contact with the skin from fifteen to thirty minutes, and the skin should then be wiped dry to remove further action of the oil.

Internally mustard acts as an irritant: it is employed as a condiment, but medicinally its only internal use is as an emetic in poisoning; a tablespoonful in a tumbler of warm water may be administered in an emergency. Poisonous doses may give rise to acute gastro-enteritis with death from collapse.

(3) **Non-volatile Irritants.**—*Cantharides* is the dried beetle *Cantharis vesicatoria*, which is widely distributed over southern Europe. It contains 0.5 to 1 per cent. of cantharidin, a crystalline substance $C_{10}H_{12}O_4$, about 12 per cent. fixed oil, and a volatile principle to which the fœtid odour of the insect is due. Cantharidin is insoluble in water, but its potassium and sodium compounds are soluble.

Action

Locally.—Cantharidin is slower in its action than the volatile oils: no change is noticed for two or three hours, then the rubefacient effect gradually arises and the burning pain is perceived, but it is much less intense than that of mustard. It is, however, for its blistering action that the drug is mainly used; the blisters are at first small and discrete, but later run together to form one big bleb. The vesicant action requires from five to ten hours to develop.

Given *internally* cantharidin produces its irritant effects along the alimentary canal; this is shown by the local production of vesicles in the mouth, vomiting, diarrhœa, severe abdominal pain, and collapse. Subcutaneous injections, as in the case of most irritant bodies (compare podophyllotoxin), produce the same results. The stools and vomited material may contain blood.

Cantharidin is absorbed, producing at first an intense vaso-constriction, and is excreted in the urine. During excretion it causes a general inflammation in the glomeruli of the kidneys, which gradually spreads among the cells of the tubules: the urine contains both blood and albumen. At the same time there will be inflammation of the bladder and urethra, accompanied by severe

pain and occasionally by priapism. Suppression of urine sometimes occurs, and is probably the result of intense renal constriction. Cantharidin has little effect on the kidney of the rabbit if the urine is alkaline, but a very violent hæmorrhagic glomerulo-nephritis results if the urine becomes acid. This suggests the use of alkalies in poisoning.

In small doses cantharidin is used as a diuretic, aphrodisiac, and emmenagogue. The so-called diuresis is probably only a constant desire to micturate, and the aphrodisiac action is due to irritation of the bladder and urethra during the excretion of the drug.

By heating oil of mustard with ammonia and alcohol a body, *thiosinamine*, is formed, $CS\begin{matrix}NH_2\\NH.C_3H_5\end{matrix}$. This substance has been recommended as an injection for the removal of scar tissue, which it is said to absorb. Reliable evidence in support of this assertion is completely lacking. The salicylate is sold under the trade name fibrolysin.

MATERIA MEDICA

Oleum Sinapis Volatile.—Containing 95 per cent. allyl isothiocyanate, C_3H_5NCS.

PREPARATION

Linimentum Sinapis.—Volatile oil of mustard, camphor, castor oil.

Cantharidinum.

Acetum Cantharidini.—0.05 per cent.

Emplastrum Cantharidini.—0.2 per cent.

Emplastrum Calefaciens.—0.02 per cent. (warming plaster).

Tinctura Cantharidini.—0.01 per cent. **Dose, 2 to 5 m.** (12 to 30 centimils).

Unguentum Cantharidini.—0.033 per cent.

Collodium Vesicans.—A solution of pyroxylin in blistering liquid.

Liquor Epispasticus.—0.4 per cent. With castor oil, resin, and acetone.

DRUGS HAVING A REMOTE ACTION ON THE SKIN

Drugs may influence the skin after absorption in a number of different ways. They may (1) alter the blood-supply to the skin. If a drug acts peripherally on a vessel, it will act on the skin-vessels in much the same way as on the splanchnic vessels; but if it produces an effect on the centre and gives rise to vaso-motor changes, the skin-vessels often do not behave like those of the rest of the body. Let us take, as an example, atropine; this drug excites the medulla and induces vaso-constriction with a rise in blood-pressure. But the skin-vessels dilate sometimes to such an extent that the face becomes flushed, and there may be a generalised

symmetrical erythema which often resembles the rash of scarlatina. Other drugs which induce vascular changes in the skin, and sometimes lead to erythematous or papular rashes, are quinine, salicin, opium, antipyrine, and chloral.

(2) The skin may be affected by alteration of the lymph-supply. Certain shell-fish cause swelling of the skin and urticaria, which is due to a direct lymphagogue action. It is probable that the rashes seen after antitoxin can be explained in this way; but, on the whole, we are ignorant of the action of drugs which have this effect. It is possible that the increased growth of the skin and keratoses sometimes seen after a prolonged exhibition of arsenic may be so explained.

(3) Certain drugs are excreted by the sweat and sebaceous glands, and during this excretion may modify the condition of the skin. Thus, the essential oils are partly excreted in this way, and can be recognised by their characteristic smell. Occasionally they cause an eruption, generally of a papular nature, which is often to be seen after taking copaiba or turpentine. The bromides are partly excreted by the skin, and during the excretion there is reason to believe that a small amount of the element bromine is set free. This sets up inflammatory lesions in the ducts of the glands, leading to acne on the face and back, and in some cases even to ulceration. Iodides also produce pustular rashes, but the rash generally clears up if the dose is increased, possibly on account of the solubility of the element iodine in a solution of iodides.

(4) The condition of the skin may be altered by influencing the nerve-supply either to the glands or the trophic nerves. Pilocarpine and physostigmine produce an active secretion of the glands by exciting the nerve-endings, whilst atropine stops all secretion by paralysing the same endings. Certain of the metals have an action on the trophic nerves. Thus, arsenic sometimes causes herpes zoster, a condition very characteristic of nerve-lesion.

(5) Some drugs alter the pigmentation of the skin. Salts of silver form a compound in the body which is deposited in certain positions, one characteristic position being under the skin, to which it gives a bluish-grey appearance. This argyria, when once established, is permanent. Arsenic also leads to pigmentation of the skin; it usually affects the covered parts of the body with accentuation about the axillæ, mammæ, and inguinal regions. It is generally regarded as due to the deposition of some broken-down blood-pigment. Antipyrine and its allies may produce also scattered pigmented patches, generally not larger than a sixpence.

CHAPTER XX

THE THEORY OF IONS—SALT ACTION—WATER

In the preceding chapters during the consideration of the action of a drug, such, for example, as strychnine, no account has been given of the action of the acid radicle with which it is combined; this is because strychnine sulphate, nitrate, and chloride all have the same effect, which the acid radicle does not appreciably modify. When we come to deal with radicles very much less toxic than that of strychnine this is not the case. Sodium chloride and sodium sulphate, for example, produce very different effects.

To appreciate these facts it is necessary to understand the "ionic theory." This assumes that certain substances, such as inorganic acids, salts, and bases, which in the dry state exist as molecules and are electrically neutral, on entering into solution split up into atoms or groups of atoms, each carrying a charge of electricity termed the electron. A monad element or radicle carries one electron, a diad two, and so on, and these electrically charged bodies are spoken of as ions, and have the value of molecules with respect to their physical phenomena. A body capable of being split up into ions is termed an electrolyte; for example:—

$$Na_2SO_4 = Na^{\cdot} + Na^{\cdot} + SO_4^{''}.$$

Electrolyte (electrically neutral). Two positive ions or kations (each with one electron). Negative ion or anion (two electrons).

The effect of an electric current on the solution of an electrolyte is to urge the anions towards the negative pole and the kations to the positive pole, where their respective electrons are neutralised. Having lost the ionic form, they undergo secondary changes, in the example given these being as follows:—

$$Na_2 + 2H_2O = 2NaHO + H_2$$
$$SO_4 + H_2O = H_2SO_4 + O$$

Elements in the molecular and the ionic condition are therefore very different things: in the latter condition the element is atomic and is charged with electricity.

No substance is resolved entirely by solution into ions: the degree of dissociation depends on many conditions, such as the nature of the solution, temperature, and concentration; some bodies —for example, proteids, sugar, urea, and alcohol—do not ionise, but preserve in solution their molecular condition unchanged.

In a 1 per cent. solution of sodium chloride about 82 per cent. of the molecules ionise.

In a normal solution, HCl, about 75 per cent. of the molecules ionise.

In a $\frac{N}{10}$ solution, HCl, about 86 per cent. of the molecules ionise.

In a $\frac{N}{1000}$ solution, HCl, about 98 per cent. of the molecules ionise.

Dilute solutions of benzoic and acetic acids, on the other hand, dissociate to less than 10 per cent.

The evidence in support of this theory is briefly as follows. Many substances when dissolved in water break up into a larger number of molecules than their chemical formula indicates. This can be shown in three ways:—(1) By *osmotic pressure*, which varies directly with the number of molecules in a solution. In the case of sugar, if one doubles the amount contained in a given solution the osmotic pressure is also doubled, but if instead of sugar an inorganic salt is employed then the pressure is more than doubled, that is, dissociation has occurred, and each ion exerts the same osmotic pressure as a whole molecule. (2) By *depression of the freezing-point.* In dilute solutions equal numbers of molecules produce equal depressions of the freezing-point. If a solution of sugar freezes at 0.2° below zero a solution containing double that quantity freezes 0.4° below zero. But with many inorganic substances this is not so, and the depression of the freezing-point reaches a maximum at two, three, or four times what might be expected. This can be explained again on the supposition that the molecules are dissociated by solution. The *boiling-point* is similarly too high with dissociable salt solutions, but rises in proportion to the number of molecules present in the case of sugar and urea. Another important proof is obtained from the (3) *electrical conductivity*, which varies exactly with the amount of ionisation. Thus, urea and sugar do not ionise, as previously shown, and they do not conduct electricity. The presence of the ions in the fluids of the body explains the ability of the tissues to transmit electricity.

The importance of this theory to pharmacology is that we now believe that it is the ions of a salt and not the whole molecule which in the animal body gives rise to pharmacological actions; and dissociable salts therefore contain two ions, each of which has a specific effect. Many facts can be cited to show the truth of this statement. Acids, for example, exert their disinfectant properties in proportion to their electrolytic dissociation, that is, to the concentration of the hydrogen ions in the solution. The hydroxides of potassium, sodium, lithium, and ammonium also disinfect according to their degree of dissociation, that is, in proportion to the (OH) ions in the solution. The toxic action of metallic salts

on living vegetable cells varies with the amount of their electrolytic dissociation. The corrosive action of K.OH is determined by the OH ion, but C_2H_5.OH has no corrosive action because the OH is not in ionic form, alcohol not being dissociable. Again $(CH_3)_2As\begin{matrix}O\\OH\end{matrix}$ (cacodylic acid) is not poisonous, and has none of the typical pharmacological actions of arsenic because this body is not dissociable into the arsenic ion. It is impossible, therefore, to describe all the salts of potassium under one head, because the action of some, such as potassium chloride, is dependent mainly on the K ion, and others, such as potassium sulphate or potassium cyanide, mainly on the negative ion.

The ions exert a definite selective action on certain tissues; for example, potassium, calcium, and barium especially attack muscle; chlorine, bromine, and iodine ions have a special affinity for nerve-cells; whilst the NH_2 ion affects mainly the cord and medulla.

It is well known that contractile tissues (heart, cilia, and plain muscle) continue to manifest their activity in certain saline solutions, and that they will not contract in pure solutions of non-electrolytes like sugar, albumen, or urea. All sodium salts will act in this way; nevertheless, it is not the sodium or positively charged ions which excite, because, if equimolecular solutions of NaCl, NaBr, NaI, and NaF are compared, it is found that their stimulating action increases progressively. For example, if an irritable nerve of a nerve-muscle preparation is placed in an isotonic solution of sodium chloride, after an hour or two the muscle begins to contract, and continues to do so for several hours. With sodium bromide the stimulation is greater, and with sodium iodide still greater. The positive ion, on the contrary, tends to destroy irritability, and its effect is roughly proportional to its valency. An ideal salt solution is one in which the stimulating ions are mixed with a certain amount of positive ions, which, like calcium, restrain activity. Ringer's solution fulfils these conditions. This ionic stimulation has been held responsible, but without sufficient proof, for amœboid movements, ciliary action, and karyokinesis. It has been suggested, further, that these ionic effects are not caused by the particles but by the electrons they carry, because in equimolecular solutions of the three groups of salts A, B, and C, whilst the members

A		B		C	
NaCl NaBr $Na.C_2H_3O_2$	Each with one negative electron.	Na_2SO_4 $Na_2.C_2O_4$ $Na_2.C_4H_4O_6$	Each with two negative electrons.	Na_3PO_4 $Na_3.C_6H_5O_7$ $Na_3.FeCy_6$	Each with three negative electrons.

of each group are about equally efficient in stimulating contractions, the trivalent are more powerful than the bivalent, which, again, are more powerful than the univalent.

The effects of an ion can only be determined by administering it with another in the form of a salt. For this purpose it should

be combined with either the Cl or Na ion, both of which are relatively inactive.

Besides their ionic action all salts and soluble bodies have a physical one, which is of no importance so long as the ionic action is strong, but of the utmost importance when this is negligible. This "salt action" only affects living tissues through changing the physical properties of the fluids contained in them or surrounding them. Osmosis is one of the physical changes included under salt action. If two equimolecular solutions are separated by a semipermeable membrane—that is, one through which water can pass, but not the dissolved substance—the osmotic pressure is equal on the two sides of the membrane, and the solutions are said to be isotonic. The term isotonic, pharmacologically, has come to mean a solution having the same osmotic tension as that of blood. If a salt solution has a higher molecular concentration it is said to be hyperisotonic, and if lower, hypoisotonic. Osmotic processes play an important part in facilitating the movement of fluids and the diffusion of salts in the organism; the epithelial cells of mucous membranes and the endothelial cells of vessels act as permeable membranes through which mineral salts constantly pass.

In the animal body, however, the molecules, instead of being passive and stable as they are in dead membranes, are made up of living cells which are in a constant state of chemical integration and disintegration. The substance in solution tending to pass between the molecules must take part in these activities, and hence one would hardly expect the laws of osmosis to be the same as when one is dealing with a dead membrane.

Some salts are absorbed into cells very readily, but others are hardly absorbed at all. Hypotonic, isotonic, and hypertonic solutions of sodium chloride are absorbed readily from the stomach and intestines. The ions K, Na, Li, Cl, Br, and I are also taken up readily enough, whilst the ion NH_4 and the non-dissociable substance urea are absorbed even more rapidly. Calcium is absorbed much more slowly, and magnesium and sulphate ions hardly at all. A solution of magnesium sulphate placed in the gut will, therefore, obey the laws of osmosis, and water will either be extracted from the tissues or given up to them until the solution is isotonic.

SALT ACTION AS EXEMPLIFIED BY SODIUM CHLORIDE

Sodium chloride enters the body daily in amounts varying from 5 to 12 grams, and is excreted in the urine. Neither the sodium nor the chlorine ion has any specific effect, and the salt is, therefore, limited to a physical action.

Action on Isolated Tissues. — *Muscle-fibre* (frog's gastrocnemius) preserves its irritability in isotonic solutions of nearly all

sodium salts, and after a short period of immersion it begins to beat rhythmically; the beating can be prevented by the addition of a little calcium salt. In hypotonic solutions fluid is absorbed by the muscle, and in hypertonic solutions fluid is withdrawn from the muscle. *Nerve-fibre* is similarly affected; if the nerve of a frog's nerve-muscle preparation is placed in an isotonic solution of sodium chloride, after a time impulses are generated, resulting in the rhythmical contraction of the muscle. The *mucous membrane and skin* undergo the same changes. Hypertonic solutions produce irritation and hardening by the extraction of water, whilst hypotonic solutions and water produce swelling and softening. Hypertonic salt solutions are used to provoke an increased flow of lymph from the wound surfaces with the object of facilitating and accelerating the natural processes of repair.

Red blood-corpuscles remain unaltered in isotonic solutions; in hypertonic solutions water is extracted and the cells become crenated, whilst in hypotonic solutions they absorb water and swell up. When the cells are surrounded by solutions of urea or ammonium chloride, whatever the concentration, they soon become distended and behave as if they had been placed in distilled water. It is obvious that there is some similarity between the cells of the intestines and the red blood-corpuscles; both, for example, absorb urea and the NH_4 ion with great rapidity, osmotic effects playing only a minor part. Salt action is, therefore, not entirely dependent on physical forces. In plants the phenomenon of plasmolysis illustrates the same effect. *Lower organisms and fish* quickly die when placed in distilled water. It has been suggested that this is due to the minute traces of copper found in ordinary distilled water, but the effect is still obtained when the water is distilled from glass and is free from all metals.

Absorption.—The question of absorption of salts from the lumen of the gut has been already considered. No satisfactory explanation of a physical nature is forthcoming to explain the reason of some ions being very rapidly absorbed, such as Na, Cl, NH_4, and others, for example, Mg and SO_4, hardly at all. Absorption varies much in different parts of the alimentary canal: it is generally greatest in the duodenum and rectum, and least in the stomach and œsophagus. Water is hardly absorbed at all in the stomach, but is rapidly absorbed from the small intestines.

Blood and Lymph.—The blood when rendered hypertonic by the direct injection of strong salt solution rapidly regains its normal composition. The osmotic attraction draws more lymph into the blood. The increased volume of the blood will, in its turn, tend to augment the flow of lymph, urine, and sweat. These vascular changes are attended by a large rise of capillary pressure in the abdominal viscera, and there is reason to believe that the increased flow of lymph is entirely the result of this pressure. Such substances form one class of lymphagogues. There is another important

class of lymphagogues comprising albumoses, crab and leech extracts, which act on the walls of the capillaries and render them more permeable.

Specific Action.—It cannot be shown that either the Cl or Na ion has any specific action. When very strong salt solutions are injected into the circulation of animals nervous symptoms are manifested, but these are probably due to withdrawal of fluid.

All salts are not, however, equally diuretic; the injection of sodium sulphate, for example, produces considerably more diuresis than an equimolecular injection of sodium chloride. This might be due to the sulphate directly stimulating the renal epithelium, but a more probable explanation is that the sodium sulphate is very much more slowly absorbed and excreted than common salt, and it, therefore, remains longer in the blood, and is thus able to attract water and so augment the hydræmic plethora.

Large quantities of water increase the excretion of nitrogen in the urine. At first this is caused by the increased movements of the body fluids. Later, however, the sulphates and phosphates in the urine are also greater, so that it is possible there may be some actual increase in nitrogenous metabolism. In correlation with this fact it has been shown that during saline diuresis the absorption of oxygen by the kidney varies with the flow of urine; from these facts it has been argued that salines directly affect the renal epithelium.

Excretion.—When diffusible substances find their way into the blood, whether directly by injection or by absorption from the alimentary canal, the flow of urine becomes greater. Bodies such as sodium chloride, potassium nitrate, potassium acetate, urea, and sugar produce this effect in a typical manner. The primary action of salts, no matter in what concentration or how they are introduced, is to increase the liquid part of the blood. Isotonic and hypotonic solutions will pass directly into blood, and hypertonic will first draw liquid from the tissue and assume the isotonic condition. So the effect comes to be the same as if an isotonic solution had been directly injected into the circulation. This causes dilatation of the renal vessels and a rise of capillary and venous pressures, and, therefore, a greater rate of blood-flow. The dilatation of the kidney-vessels is peripheral in origin, since it still occurs after cutting the renal nerves, and it varies in a fairly constant manner with the secretion of urine. The diuretic properties of salines injected into the blood-stream depend on their power of attracting water, and, therefore, vary with their molecular weights or the amounts of hydræmic plethora they induce. It seems probable that this hydræmic plethora first induces the changes in the vessels, and as a result of this the diuresis follows. In any case the salts can hardly be secreto-motor, since the diuresis comes to an end when only a small amount of them has been excreted.

The urine is rich in the particular salt taken, but all the salts are increased, for the serum cannot rid itself of one salt without losing some of its other salts. And so it is seen that animals and man living on a herbivorous diet, one rich in potash, have a craving for common salt, whilst a carnivorous diet does not create this desire. An exception to this is the injection of sodium sulphate into the blood, which produces a urine containing hardly any chloride.

MATERIA MEDICA

Aqua Destillata.
Sodii Chloridum. Dose, ½ to 1 oz.

MINERAL WATERS

It has been often noted that the action on patients of mineral waters at their source is different from that produced by the bottled water or by the artificially prepared water when taken at home. This must unquestionably be attributed to the altered hygienic conditions, rest, food, habits, scene, diet, and exercise. Many of the effects which are obtained may also be due to the imbibition of large quantities of water.

The various mineral waters can be classified as follows :—

(1) Those containing much sodium chloride.

(2) Those containing many non-absorbable ions, such as magnesium sulphate.

(3) Those containing much CO_2.

(4) Sulphur waters.

(5) Iron waters.

The most typical saline water is, of course, sea-water. This contains about 2.7 per cent. NaCl, and a total of from 3.5 to 4 per cent. of mixed salts. The salts in aperient waters consist principally of magnesium sulphate and sodium sulphate ; Hunyadi János water can be regarded as a typical example. Carbonated waters may, in the first place, be simple, such as Apollinaris or the artificially prepared soda-water ; they owe their action to the carbonic acid gas they contain, which irritates the stomach and slightly increases the rate of absorption. Some of these waters contain alkalies, such as sodium bicarbonate ; such are the waters of Vichy and Ems. Others, again, contain sulphates, and are, therefore, slightly aperient ; this is the case with the saline waters of Carlsbad. Sulphur waters contain free sulphuretted hydrogen and other sulphides—Aix-les-Bains contains 0.0003 per cent. free sulphuretted hydrogen : they are mildly irritant to the skin and gastro-intestinal mucous membrane. The amount of iron in the chalybeate waters varies from 0.01 to 0.13 FeO per litre. Their action resembles that of iron salts.

CHAPTER XXI

CERTAIN POSITIVE IONS

Potassium, Lithium, Ammonium, Calcium, Magnesium

POTASSIUM

Potassium salts are found in the ash of all parts of the animal body They are absorbed into the system in considerable quantities with the food, some people taking as much as 50 grams of potash a day. It is obvious from this fact that the potassium ion has very little specific action when a potash salt is administered by the mouth. The explanation of this is not difficult: the salts of potash diffuse very readily into cells, more readily than those of sodium but not so rapidly as ammonium salts, and they are excreted proportionally quickly by the kidneys. The elimination is, indeed, so rapid that, like curare and the NH_4 ion, no evil effects follow its administration by the mouth, because the excretion can more than keep pace with the absorption. But subcutaneous or, more certainly, intravenous injections act as a powerful poison to the heart and central nervous system, and potassium salts in a mild degree may be regarded as general protoplasmic poisons.

The only effect then of potassium salts given by the mouth is a salt action.

Heart.—Ringer has shown that the presence of a little potassium salt in a saline solution favours the efficient beating of the frog's heart. When the amount of potassium is large the systole becomes shorter and weaker, and the heart eventually stops in diastole. This is due to the direct action of the K ion on the muscle, and it can be antagonised by the application of a calcium salt if the effect has not been carried too far.

The injection of small doses of potash salts into the circulation of mammalia produces an immediate fall of blood-pressure and some cardiac slowing; this is followed almost immediately by a rise of pressure above normal and slight quickening of the heart-beat. Larger injections cause the heart to stop beating in diastole. The action is uninfluenced by the previous administration of atropine (Fig. 79). Potassium is poisonous to the heart in concentrations of 0.08 per cent. or more.

Voluntary Muscle.—If potassium chloride is applied directly to a frog's gastrocnemius there is a similar depressant action.

At first, for a very brief period, the height of the contractions in response to single induction shocks is slightly increased, but soon it becomes smaller, till ultimately the contractile power is lost completely (Fig. 80). This effect on muscle is antagonised by barium and calcium salts, or by veratrine.

When a frog's sartorius is placed in an isotonic solution of potassium chloride, spontaneous and rhythmical contractions of the

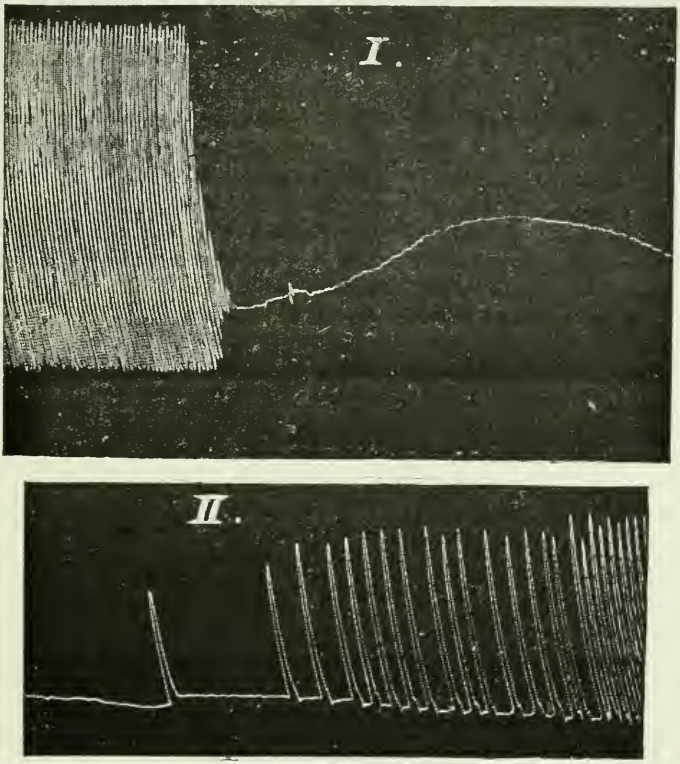


FIG. 79.—RECORD OF A RABBIT'S HEART PERFUSED WITH RINGER'S SOLUTION.

Tracing I. shows the effect of adding KCl to the fluid (0.2 per cent.). Tracing II. shows gradual recovery of the heart when the KCl is withdrawn.

muscle are produced, but they are feebler and do not last so long as those caused by sodium chloride.

Plain Muscle.—Large injections of potassium chloride diminish the automatic movements of plain muscle throughout the body. Given by the mouth they are more irritant to the stomach than sodium salts and more readily cause vomiting.

The **central nervous system** is depressed by large doses of potash. There are great muscular weakness, apathy, and diminution

of the reflexes: death is caused by paralysis of the medulla, and may be preceded by asphyxial convulsions.

Excretion.—Potassium is excreted in the urine, and the whole toxicity of normal urine is due to the presence of the K ion. The administration of potash salts by the mouth increases the flow of urine more than the corresponding sodium salts.

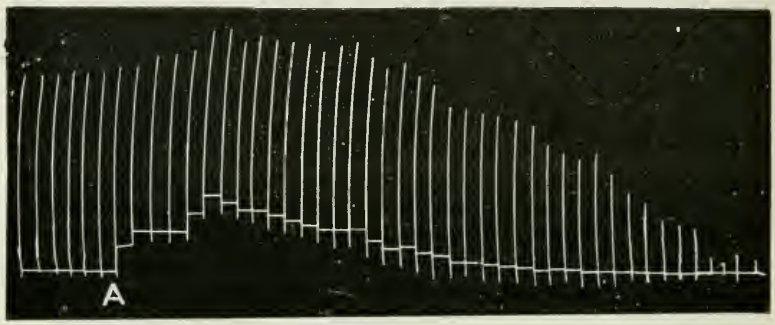


FIG. 80.—RECORDS OF THE CONTRACTION OF A FROG'S GASTROCNEMIUS PRODUCED BY SINGLE INDUCTION BREAK-SHOCKS.

At A 0.8 per cent. KCl was substituted for normal saline solution. The contractions became more and more feeble till death occurred. The contracture which occurs at first is due largely to osmotic effects. Time between two shocks = about ten seconds

MATERIA MEDICA

1. **Liquor Potassæ.**—5 per cent. **Dose, 10 to 30 m.** (6 to 8 decimils) diluted.
2. **Potassa Caustica.**
3. **Potassii Bicarbonas. Dose, 5 to 30 grs.** (3 to 20 dcgrms.).
4. **Potassii Carbonas. Dose, 5 to 20 grs.** (3 to 12 dcgrms.).
5. **Potassii Sulphas. Dose, 15 to 45 grs.** (1 to 3 grms.).
6. **Potassii Nitras. Dose, 5 to 20 grs.** (3 to 12 dcgrms.).
7. **Potassii Acetas. Dose, 15 to 60 grs.** (1 to 4 grms.).
8. **Potassii Citras. Dose, 15 to 60 grs.** (1 to 4 grms.).
9. **Potassii Tartras. Dose, 30 to 60 grs.** (2 to 4 grms.) (diuretic); 2 to 4 drs. (8 to 16 grms.) (purgative).
10. **Potassii Tartras Acidus.**—Cream of Tartar. **Dose, 15 to 60 grs.** (1 to 4 grms.) (diuretic). Larger doses may be given as a purgative.
11. **Potassii Chloras. Dose, 5 to 15 grs.** (3 to 10 dcgrms.).

PREPARATION

Trochiscus Potassii Chloratis.—3 grs. in each (0.2 grm.).

Potassium is present also in the following salts, whose action in no way depends on the presence of the K ion:—Potassium iodide, bromide, permanganate, bichromate, and in soft soap or potassium oleate.

LITHIUM

Lithium is found in the ash of plants and animals, and is a constituent of some mineral waters, such as those of Carlsbad, Vals, and Baden Baden. It was originally introduced into medicine as a solvent for uric acid, and it was hoped that by its agency urates deposited in the joints might be absorbed. But to act as a solvent for uric acid the lithium must occur in a certain concentration, and this concentration can never be reached in the animal body without toxic symptoms supervening.

Lithium is absorbed from the stomach very rapidly, and exerts a potassium-effect on the heart and voluntary muscles, but in a smaller degree. Large doses, whether administered subcutaneously or by the mouth, cause nausea, vomiting, diarrhœa, and subsequently acute gastro-enteritis, followed by emaciation, weakness, and death from collapse. This action is characteristic of the lithium salts, and is brought about after the injections by the excretion of some of the drug into the gut. Lithium carbonate in 20-gr. doses has been known to lead to disturbance of the alimentary tract.

Lithium is excreted in the saliva, stomach, and bowels, but principally in the urine. It may be detected in the urine within fifteen minutes from the time of its administration, and traces can be still found five or six days after a single dose. The excretion by the kidneys is accompanied by no irritation, and the diuresis is the result of salt action, and is no greater than that produced by an equal quantity of common salt. Lithium salts render the urine alkaline, and thus act like other fixed alkalies.

MATERIA MEDICA

1. **Lithii Carbonas.**—Li_2CO_3. **Dose, 2 to 5 grs.** (12 to 30 ctgrms.).
2. **Lithii Citras. Dose, 5 to 10 grs.** (3 to 6 dcgrms.).
3. **Lithii Citras Effervescens.**—Containing tartaric acid and sodium bicarbonate. **Dose, 60 to 120 grs.** (4 to 8 grms.).

AMMONIUM

The NH_4 ion may be conveniently considered along with the K, Na, and Li ions, with which it has many actions in common; it differs from them, however, in that it stimulates the central nervous system, and this effect also appears, though to a smaller degree, in the substituted ammonias, the amines and amides. Ammonium chloride is absorbed rapidly from the stomach and intestines, probably more quickly than any other salt, but when the NH_4 is combined with a non-penetrating negative ion, as in $(NH_4)_2SO_4$, it is absorbed very slowly. These facts are in harmony with what is known concerning the action of such salts on red blood-corpuscles. Ammonium chloride penetrates red-blood cells rapidly, but ammonium sulphate is taken up very slowly.

The action of ammonium, like that of potassium, varies with the mode of administration. When it is injected either intravenously or subcutaneously there is a pronounced effect on the central nervous system, but when the drug is given by the mouth this is wanting, on account of its very rapid excretion and conversion in the body to urea.

Central Nervous System.—If ammonium chloride is injected into either frogs or mammals the reflexes are soon exaggerated, and ultimately strychnine-like convulsions ensue. These are reflex, and are not abolished by division of the cord, but cease as it is destroyed from above downwards: during the paroxysms respiration ceases and the blood-pressure rises. Such convulsions differ from those seen in strychnine poisoning in that the muscles of the head are also involved, which shows that the brain is affected; and, moreover, they are never of so violent a character. About 0.15 gram ammonium chloride per kilo body-weight will induce convulsions in a mammal, but it takes 0.5 gram per kilo to induce death. Such a large difference as this is not found with strychnine (Fig. 74).

The stimulation of the medulla produces other conditions. Respiration is quickened and sometimes deepened; the effect is still obtained after section of the vagi, and is, therefore, due to excitation of the centre. The peripheral arterioles are constricted and the blood-pressure goes up; this is due also to central stimulation, since it is hardly appreciable if the salt is injected after the spinal cord has been cut. Rise in blood-pressure from this cause must not be confused with that which occurs during the convulsions. The temperature is slightly raised by stimulation of the corpus striatum, but when the convulsions begin the rise of temperature is accelerated.

The heart is little affected; small doses, as is the case with potash and lithium, slightly quicken the beat from a direct action on cardiac muscle.

Muscle and Nerve.—Ammonium has an action upon voluntary muscle corresponding with that of potassium and lithium. In the frog it paralyses ultimately the motor never-endings, in which it resembles the strychnine group of drugs. This explains why in this animal the convulsions, which are powerful at first, soon weaken and later cease. The nerve-endings are not paralysed in mammals. (*See* Convulsants.)

Secretions.—The flow of bronchial mucus is greater. The NH_4 ion is regarded as a valuable expectorant, because it increases the flow of mucus and also aids in its expulsion. It acts, in the first place, by irritating the mucous membrane of the stomach, and so reflexly exciting the vagus nerves supplying the mucous glands of the respiratory tract. But any drug, like apomorphine, which excites the medulla increases bronchial secretion through the vagus nerve; and some of the action of ammonium, especially when it is injected, may be due to this cause.

Ammonium hydrate and carbonate differ from the other salts

of ammonia in that the gas NH_3 evaporates very readily from their watery solutions, and hence many of the properties of these bodies are due to the OH ion, and will be considered with the alkalies. Since, however, ammonium carbonate is employed for inhalation in the form of smelling salts, its action must be considered briefly.

That portion of the nasal septum which is high up and towards the back is particularly susceptible to all forms of excitation: the reflexes which can be produced by excitation at this spot are of a protective nature, the object being to prevent the entrance or absorption of irritant particles or vapours into the lungs. Thus, irritation of the nasal mucous membrane with such irritant substances as ammonia or bromine may produce (1) sneezing and coughing, (2) closure of the glottis, (3) arrest or slowing of the respiration, (4) cardiac inhibition, (5) vaso-constriction, (6) bronchial constriction. All these effects are reflexes, mostly medullary. Ammonia vapour is often inhaled, therefore, in fainting or collapse, in order reflexly to stimulate the medullary centres (Fig. 75).

Excretion.—Ammonium carbonate is converted to urea and excreted in the urine. This change is brought about in the liver, as can be shown by artificial perfusion with defibrinated blood containing ammonium carbonate. Ammonium carbonate increases the amount of glycogen stored up in the liver. The chloride and other stable ammonium salts are excreted mostly unchanged in carnivora, though some is converted to urea. Ammonium citrate is converted in the tissues to the carbonate, and is, therefore, excreted as urea, and so does not add to the alkalinity of the urine. This should be compared with the citrates and tartrates of the fixed alkalies, such as potassium citrate, which are converted in the tissues to the carbonate, and are excreted in this form, thus increasing the alkalinity of the urine. Ammonium salts rather tend to render the urine more acid.

MATERIA MEDICA

1. **Liquor Ammoniæ Fortis** (32.5 per cent. NH_3 dissolved in water).

PREPARATIONS

1. **Linimentum Camphoræ Ammoniatum** (with camphor alcohol and oil of lavender).
2. **Linimentum Hydrargyri.**
3. **Spiritus Ammoniæ Aromaticus.** *See* Ammonium carbonate.
4. **Spiritus Ammoniæ Fetidus.** *See* Asafetida.
5. **Tinctura Guaiaci Ammoniata.** *See* Guaiacum.

2. **Liquor Ammoniæ.**—10 per cent. solution.

PREPARATIONS

1. **Linimentum Ammoniæ.**—With oil, making an oleate of ammonium.
2. **Tinctura Ergotæ Ammoniata.**
3. **Tinctura Opii Ammoniata.**
4. **Tinctura Quininæ Ammoniata.**
5. **Tinctura Valerianæ Ammoniata.**

3. **Ammonii Chloridum.** **Dose, 5 to 20 grs.** (3 to 12 dcgrms.).
4. **Ammonii Carbonas.** **Dose, 3 to 10 grs.** (2 to 6 dcgrms.) (expectorant). Larger doses are used to cause vomiting.

PREPARATION

Spiritus Ammoniæ Aromaticus (spirit of sal volatile).—Contains ammonia, ammonium carbonate, and some volatile oils in alcohol.

Dose, 20 to 40 m. (15 to 25 decimils) for repeated, **60 to 90 m.** (4 to 6 mils) for single administration.

5. **Liquor Ammonii Acetatis.** **Dose, 2 to 6 drs.** (8 to 24 mils).
6. **Liquor Ammonii Citratis.** **Dose, 2 to 6 drs.** (8 to 24 mils).

The action of ammonium benzoate and ammonium bromide does not depend upon the ammonium ion.

CALCIUM

Calcium phosphate forms three-fourths of the total mineral matter in the body; it is mostly contained in the bones, to which it gives rigidity. It is present also in all soft tissues and in the blood; in the latter it is held in solution by the albuminous constituents. Calcium is a necessary constituent of all protoplasm, and is essential to the action of some ferments, such as rennet and fibrin-ferment in the case of the clotting of milk and blood respectively. The lime taken into the body with the various foodstuffs, especially flesh, vegetables, yolk of eggs, and milk, is sufficient for the needs of the organism.

Lime water is used for mixing with milk, as it stops the formation of thick curds in the stomach, and so prevents vomiting, especially in children. Lime salts, more especially chalk, are used in diarrhœa. They act physically in much the same way as bismuth salts, forming a coat of insoluble salt over the mucous membrane.

The Effects of Lime Starvation.—Pigeons and other birds when fed on foods containing little or no lime quickly show an alteration in their bones, which become thinner and more brittle. In mammalia any condition which causes a prolonged and impaired absorption of calcium leads to an alteration in the composition of the skeleton, and especially is this the case in young animals, where the growth of the bones is very much restricted. But though in lime starvation but little bone is developed, that which is formed contains its usual percentage of lime and differs little from normal bone.

It has been claimed that deprivation from lime salts is the cause of rickets—a disease of ill-nourished children in which the amount of calcium in the bones is very deficient. In rickets there is an impaired growth of bone, not in amount, for this may be excessive, but in the quality of the bone formed; and the deficiency of calcium is only secondary to this change, for the other parts of the body

always retain their normal percentage of lime. This can hardly be due to a diminished capacity for absorption of lime, since rickety children when given lime salts excrete as much in the urine as normal children, that is, absorption is normal.

If sea organisms are placed in pure solutions of common salt in the same concentration as it occurs in sea water they die very quickly, but they survive if a trace of calcium chloride and potassium chloride are added to the water. Ringer* has shown, by numerous observations on fish, tadpoles, cilia, skeletal muscle, and heart, the essential importance of these salts to the organism, even the minute quantities present in river water being sufficient to keep fish alive for weeks which would die very quickly in distilled water. In experiments of this type great care is required in the selection of a distilled water. The ordinary commercial distilled water contains traces of copper and other protoplasmic poisons, which quickly destroy tadpoles, tubifex, and cilia. The water should be freshly distilled from glass vessels. The excitability of voluntary muscle is greatly increased by the removal of the calcium ions. The fibrillary twitching seen in poisoning by oxalic and citric acids is due to the removal of calcium.

Absorption and Excretion.—Lime salts are absorbed in small quantities from the stomach and duodenum. Their absorption is facilitated by fats: the lime combines with the fatty acid and forms a soap of calcium, which is more readily taken up by the intestinal epithelium. The bulk of the absorbed lime is excreted into the large intestine, but a small proportion is eliminated in the urine. The excretion by the kidneys is increased during starvation, and is greater during rest than exercise. The percentage of calcium in the blood is not increased by the administration of lime by the mouth to normal men.

Action on Ferments.—The coagulation of milk by rennet, and blood by fibrin-ferment, are analogous phenomena. In both instances calcium salts are a necessity, and the clotting may be delayed by the addition of a small quantity of oxalate. Taking the case of milk first, when the rennet is added the caseinogen is converted into "soluble casein," and this is precipitated by the calcium as a curd. The coagulation of the blood, that is, the transformation of fibrinogen into fibrin, requires the interaction of a lipoid and a calcium salt: as a result of this interaction a ferment is obtained which, under suitable conditions, produces the fibrin. On account of its effect on the clotting-time of the blood, calcium is used in the treatment of hæmorrhage, especially in the conditions known as hæmophilia and purpura hæmorrhagica.

* One formula for a Ringer's solution is the following:—

100 c.c., 0.75 per cent. NaCl.	2.5 c.c., 0.5 per cent. $NaHCO_3$.
5 c.c., 0.25 per cent. $CaCl_2$.	0.75 c.c., 1 per cent. KCl.

Instead of the $CaCl_2$, the solution may be saturated with $Ca_3P_2O_8$.

For this purpose organic salts of calcium, such as the lactate, are preferred to the more irritant salts, as the chloride.

Specific Action.—Calcium, like barium, has a specific action on all forms of muscle, but its effect is much weaker than that of the latter drug. It increases the contraction and prolongs the relaxation of a frog's gastrocnemius; it constricts vessels and produces a barium-like effect on the frog's heart, that is, the contraction is prolonged and the relaxation retarded. Further, these effects are antagonised by potash salts, and *vice versa* the effect of potash on the frog's heart and voluntary muscles is antagonised by the addition of lime. Calcium is also antagonistic to magnesium; possibly it forms a triple phosphate with the magnesium, which is thereby rendered innocuous.

It has been suggested that the effects produced by excitation of the vagus and sympathetic nerves could be explained by changes

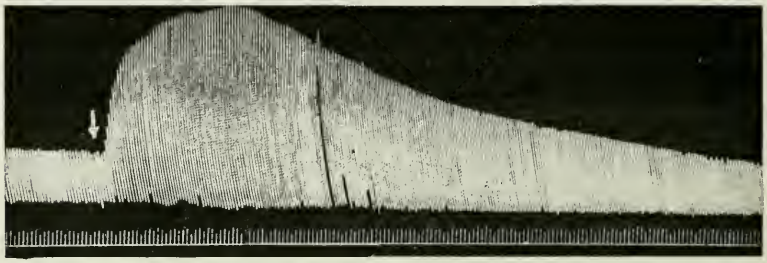


Fig. 81.—Movements of Isolated Rabbit's Heart perfused with Locke's Solution.

At the arrow 5 mgrms. of calcium chloride were administered. Time in seconds.

in the calcium and potassium content. Calcium-precipitating substances administered to frogs destroy the vagus inhibitory powers, and to cats strongly diminish the excitability of the heart-vagus, but the excitability of the pelvic nerve, the chorda tympani, and the cervical sympathetic are not diminished. On the other hand, certain chemical substances (pilocarpine, atropine, and adrenalin) acting at the periphery produce an increased action. These two effects—the depression of the nerve to faradization and the increased susceptibility to certain chemicals—are not antagonistic. Pilocarpine, adrenalin, and atropine we know produce an increased action after section and degeneration of the nerves to the tissues upon which they act. This evidence tends to show, then, that the absence of calcium causes a block at the nerve-endings γ. In other words, the γ is paralysed, whilst the β is hypersusceptible to chemical stimuli.

It is doubtful whether the Ca ion has any specific action when it is administered as a salt by the mouth. Possibly this is due to the scanty and very slow absorption. When the salts are injected

FIG. 81A.—ANTAGONISM OF Ca ION TO K ION.

Isolated rabbit's heart perfused with Ringer's solution. At A a small dose of potassium chloride was added to the Ringer, and at B a dose of calcium chloride. The antagonistic action is well shown.

To face p. 338

directly into the circulation, the heart beats more vigorously, the vessels constrict, and the blood-pressure rises (Fig. 81).

But the most important specific action of calcium is its power to retard inflammatory processes. If a little abrin or mustard oil be applied to the conjunctiva, œdema and intense inflammation follow; but the previous subcutaneous injection of a calcium salt prevents this effect. Or again, sodium iodide or thiosinamine injected into some animals cause effusion into the pleura and pericardium and often pulmonary œdema, but calcium salts again prevent such effusion. These salts then have an important action in limiting inflammatory exudations in the body, and they have been employed successfully in urticaria and other skin diseases. How calcium produces these effects is not known, but it is believed by some to be associated with its power of precipitating many organic colloids, especially lecithin.

MATERIA MEDICA

1. Calx.—Lime. CaO.
2. Calcii Hydras.—Slaked lime. $Ca(OH)_2$.
3. Creta Præparata.—$CaCO_3$. Dose, 10 to 60 grs. (1 to 4 grms.).

PREPARATIONS. 1. Hydrargyrum cum Cretâ. *See under* Mercury. 2. Mistura Cretæ.—Prepared chalk, suspended by gum. Dose, ½ to 1 oz. (15 to 30 mils). 3. Pulvis Cretæ Aromaticus.—With cinnamon nutmeg and cardamom. Dose, 10 to 60 grs. (6 to 40 decgrms.). 4. Pulvis Cretæ Aromaticus cum Opio. *See* Opium.

4. Calcii Carbonas Præcipitatus.—Precipitated chalk. Dose, 15 to 60 grs. (1 to 4 grms.).

PREPARATIONS. 1. Liquor Calcis.—Lime water. 1 gr. to 1 oz. Dose, 1 to 4 oz. (30 to 120 mils). 2. Liquor Calcis Saccharatus.—Lime water and sugar. Dose, 15 to 60 m. (1 to 4 mils). 3. Linimentum Calcis.—Equal parts of lime water and olive oil. Calcium oleate is formed. *Carron oil* is composed of equal parts of lime water and linseed oil.

5. Calcii Phosphas.—$Ca_3(PO_4)_2$. Dose, 5 to 15 grs. (3 to 10 decgrms.).

PREPARATION. Syrupus Calcii Lactophosphatis.—Calcium phosphate, about 1 in 40. Dose, ½ to 1 dr. (2 to 4 mils).

6. Calcii Chloridum.—$CaCl_2,2(H_2O)$. Dose, 5 to 15 grs. (3 to 10 decgrms.).
7. Calx Sulphurata. *See under* Sulphur.
8. Calx Chlorinata. *See under* Chlorine.
9. Calcii Hypophosphis. Dose, 3 to 10 grs. (2 to 6 decgrms.).
10. Calcii Lactas.—Soluble in water to 1 in 15. Dose, 10 to 30 grs. (6 to 20 decgrms.).

MAGNESIUM

All the salts and bases of magnesium are converted to the acid carbonate in the small intestine thus :—$MgSO_4 + Na_2CO_3 + H_2O + CO_2 = Mg(HCO_3)_2 + Na_2SO_4$. When the chloride is injected intravenously, it gives rise to a potassium-like effect on the heart and central nervous system. Taken by the mouth, however, it is absorbed in very small amount (not enough to produce the specific ionic action), and its cathartic effect depends on this fact and the subsequent osmotic changes which it induces. When 1½-gr. doses of $MgSO_4$ are injected subcutaneously into man they slightly increase peristalsis, and so may produce purgation. This, of course, is quite a distinct action from that which obtains when the drug is administered by the mouth, for any irritant substance injected under the skin will induce increased peristalsis.

The injection of large doses of magnesium subcutaneously into animals causes a general paralysis of the central nervous system, the medulla being the last to be affected. At this time the voluntary muscles and heart are not appreciably affected. Complete paralysis of the central nervous system in animals can be obtained by injecting magnesium chloride to the extent of about one gram per kilo body-weight. Magnesium salts have been injected into the theca of the spinal cord to produce spinal analgesia ; the effect resembles that of cocaine, but is more lasting and much more dangerous. A complete and rapid recovery from this narcosis is brought about by the injection of calcium into a vein. The explanation may be that the calcium and magnesium form a triple phosphate which ionises little and is rapidly excreted.

MATERIA MEDICA

1. **Magnesii Sulphas.**—$MgSO_4,7H_2O$. Epsom salts. **Dose, 30 to 90 grs.** (2 to 6 grms.) for repeated, ¼ to ½ **oz.** (8 to 16 grms.) for single administration.

PREPARATION. **Mistura Sennæ Composita.**

2. **Magnesii Sulphas Effervescens.**—With tartaric acid, citric acid, and sodium bicarbonate. **Dose, 60 to 180 grs.** (4 to 12 grms.) for repeated administration ; for a single administration ½ **to 1 oz.** (16 to 32 grms.).

3. **Magnesia Ponderosa. Dose, 5 to 20 grs.** (3 to 12 decgrms.) repeated ; **30 to 60 grs.** (2 to 4 grms.) single.

4. **Magnesia Levis. Dose,** same as heavy magnesia.

5. **Magnesii Carbonas Ponderosus.**—$(MgCO_3)_3,Mg(OH)_2,4H_2O$. **Dose,** like magnesia.

PREPARATION

Liquor Magnesii Bicarbonatis.—Fluid magnesia with carbonic acid gas under a pressure of three atmospheres.

Dose, 1 to 2 oz. (30 to 60 mils).

6. **Magnesii Carbonas Levis.**—$(MgCO_3)_3,Mg(OH)_2,4H_2O$. **Dose,** like magnesia.

CHAPTER XXII

ACIDS AND ALKALIES

DILUTE ACIDS

SULPHURIC, NITRIC, HYDROCHLORIC, NITROHYDROCHLORIC, PHOSPHORIC, ACETIC, LACTIC, TARTARIC, CITRIC, AND SULPHUROUS ACIDS

THE dilute acids owe their acidity and their action to the presence of the H ion. Some acids, such as hydrocyanic, have so toxic a negative ion that the acid action may be neglected entirely; whilst in others, such as salicylic acid, where the dissociation is very small, the acid effect is too insignificant to be of much account, so that such acids act in the same way as their salts.

Dilute acids owe their action to the power of neutralising alkalies, although more concentrated acids produce a further effect by precipitating proteins and extracting water from the tissues. Most living matter has a slightly alkaline reaction, and dilute acids, therefore, behave as general protoplasmic poisons by destroying this alkalinity: exceptions to this rule are found in some of the filamentous fungi, such as penicillium, which thrive in an acid medium. Hence, dilute acids exert depressant effects upon isolated organs.

On striped muscle even such dilute solutions of hydrochloric acid as 1 in 20,000 rapidly diminish the height of contraction on electrical stimulation, and produce some contracture. On plain muscle 1 in 10,000 lactic acid will serve to check the automatic waves and induce considerable relaxation (Fig. 82). When applied to the frog's heart they shorten the duration of systole and diminish its force, and the heart ultimately stops in diastole. If vessels are perfused artificially outside the body with an acid solution constriction invariably follows: such dilute solutions as 1 in 20,000 hydrochloric or 1 in 10,000 lactic acid serve to produce a strong constriction. It is not probable, however, that constriction follows when dilute acids are administered by the mouth, since we know that in life the blood is always alkaline. In these effects on isolated organs acids and alkalies counteract one another, so that, for example, a heart-beat much diminished in force by acids will be restored by alkalies. In all these effects mineral acids are much more active than organic acids, but phosphoric acid is much less active than the other mineral acids; the difference in action is

solely one of dissociation. All acids have an antiseptic action which varies with the dissociation, that is, the number of H ions in the solution. Hydrochloric acid, of a strength equal to that in which it is present in gastric juice, destroys the majority of bacilli; but even as a 2 per cent. solution it has little effect on anthrax and other resistant spores.

Alimentary Canal.—Dilute acids possess an important action on the digestive tract. In the mouth they have a sour, somewhat astringent taste, and reflexly increase the flow of saliva. Pawlow has shown that a dog with a submaxillary fistula secretes saliva under the influence of the following stimuli:—(1) The mere sight of food (psychical). (2) The act of eating. (3) Touch, as by

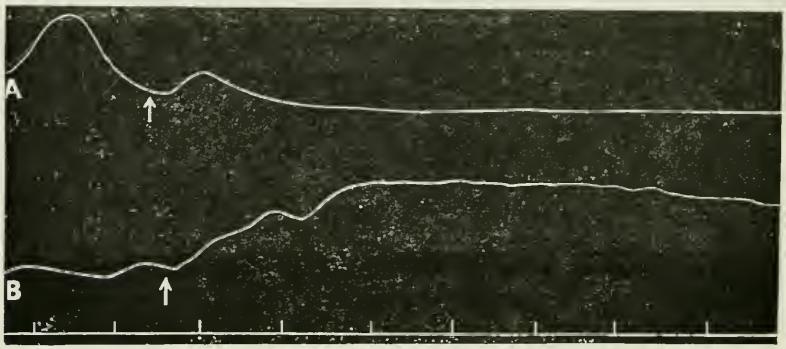


FIG. 82.—THE ACTION OF ACID ON PLAIN MUSCLE.

The figure shows two records of the movements of a frog's stomach. A shows the effect of 1 in 1000 lactic acid applied at the arrow. Note the diminution of tonus and cessation of movements. B shows the action of a 1 in 100 solution of the same acid. In this case the tonus is increased (upstroke = contraction). Time = half-minutes.

putting fine sand in the mouth. (4) Chemical stimulants, notably acids and bitters. Acids then are sialagogues as regards the submaxillary saliva. The parotid gland, in contradistinction to the submaxillary, shows a decided selective power in the choice of a suitable stimulus, but it is excited reflexly by acids and gives out a special saliva, which is particularly rich in proteids, but the significance of which we do not understand.

Acids do not affect the secretion of the gastric juice, but they may be administered with advantage in those cases where there is a deficiency in the secretion of hydrochloric acid, such as is known to occur in cancer of the stomach. Other acids besides hydrochloric produce these effects. The most important action of acids in the alimentary canal is their excitation of the pancreas. Dilute acid injected into the circulation of an animal causes no increase in the secretion of pancreatic juice, but if it is injected into the duodenum or placed in the stomach the pancreas begins to secrete in two or three minutes. If an acid extract of the mucous membrane

of the duodenum is boiled, neutralised with sodium carbonate, and filtered, it will, on injection into the blood, produce a great augmentation of the pancreatic secretion. The "*secretin*" so formed is produced naturally in the body, and is specific to the pancreatic cells only. The effect is directly on the gland-cell. The action of the acid is to render the *prosecretin* of the duodenal cells soluble when it becomes secretin (p. 444).

Excretion.—The mineral acids are rapidly absorbed from the alimentary canal, and are converted to salts. They render the blood less alkaline, although during life it never becomes acid. This reduced alkalinity is more marked in herbivorous animals in which the acid is excreted in combination with the fixed alkalies potassium and sodium. In carnivorous animals and man the effect on the blood is less decided, and the acids are excreted in the urine mainly as ammonium salts, so that the fixed alkali is saved and forms a second line of defence against the acid. Nevertheless, the increase of fixed alkalies in the urine, even in carnivora, is nearly sufficient to neutralise the acid absorbed.

The name "acidosis" ought to mean increase of acidity; that is, of concentration in hydrogen ions. Unless the respiratory centre is extremely insensitive, this is only permitted to occur to a very small degree, because of the increase in pulmonary ventilation due to stimulation of the centre. The acid acts on the reserve alkaline carbonate and liberates CO_2, which excites the centre so that in the majority of conditions of acidosis the reaction of the blood is normal, although the alkali reserve is lowered.

Although it needs a change in the C_H of the body fluids to produce an immediate result of any sort, it is quite wrong to speak of *a depletion of the alkali reserve* as though it were of no importance. An individual displaying diminished alkali reserve is not in a position of equal safety with one in whom the reserve is normal. The former, unlike the latter, may, for instance, become perceptibly dyspnœic on slight exertion.

There is an increase in the nitrogenous excretion of the urine which is entirely due to ammonia, for the urea is slightly diminished in amount. This ammonia may be derived from a greater breakdown of protein, or it may be abstracted from the ammonia of the portal blood, and so interfere with urea formation by the liver. The evidence points to the view that the free acid combines with ammonia and thus prevents it from undergoing further chemical change into urea. The urine, as already mentioned, contains, also, an increased amount of fixed alkali. Dilute acids produce diuresis as the result of salt action, and this may account for some of the increased excretion of sodium. Little or no free acid is excreted, but the urine is rendered more acid by the formation of acid salts, which cause considerable irritation of the kidneys and the mucous membrane of the genito-urinary tract.

Sulphuric Acid

Dilute sulphuric acid is used as an astringent in bleeding from mucous surfaces; but it has no action on the lower bowel, since acids are quickly neutralised and absorbed, nor does it possess any astringency after absorption. It is administered in cases of poisoning by lead, and acts by forming the insoluble $PbSO_4$. Sulphuric acid is used to aid in the solution of quinine sulphate, but it should be remembered that its presence in medicines favours the growth of moulds.

In poisoning by strong sulphuric acid, the symptoms consist of charring of tissues, intense pain, vomiting of coffee-coloured fluid, and death from collapse in a few hours. The acid acts by its intense attraction for water and its power of precipitating albumen. Oxide of magnesia or white of egg may be used as an antidote.

Nitric Acid

Nitric acid is used externally in the destruction of warts, moles, and to stimulate sluggish ulcers. When taken internally it was thought at one time to have a specific action on the liver, but this is fallacious. Its action on mucous surfaces is superficial only, because it cannot re-dissolve the albumen which it precipitates, and which limits its further penetration. Nitric acid differs from sulphuric acid in that it stains the skin yellow, it does not cause charring, and, as fumes are readily given off, it is more likely to affect the respiratory passages.

Nitrohydrochloric Acid

This acid contains HNO_3, HCl, Cl, NOCl, and HNO_2. The dilute acid only is used in medicine; it has a reputation in the treatment of certain cases of dyspepsia, and is employed also as a cholagogue, though proof of the latter action is wanting. The acid should be recently prepared.

Hydrochloric Acid

Hydrochloric acid is less corrosive than sulphuric or nitric, but, being a gas, is more apt to attack the respiratory passages. It is the acid which is generally employed in dyspepsia.

Phosphoric Acid

Phosphoric acid has no properties beyond those possessed by the other mineral acids. When diluted it makes an agreeable drink, but has none of the actions of free phosphorus.

Acetic Acid, $CH_3.COOH$

Glacial acetic acid is a caustic; when applied to the skin it dissolves the epithelium, and is used to destroy warts. When diluted it possesses the astringent properties of the dilute mineral acids, so that vinegar has been injected into the uterus as a hæmostatic in post-partum hæmorrhage. Its prolonged administration internally produces a diminution in the number of the red blood-corpuscles, leading to anæmia and loss of weight.

Lactic Acid, $CH_3.CH\begin{matrix}OH\\COOH\end{matrix}$

Lactic acid as a 50 per cent. solution is largely employed for direct local application to tubercle of the larynx, throat, and tongue. Taken internally this acid sometimes produces pains in the joints it was at one time believed to be the cause of rheumatism.

Recently Metchnikoff has suggested the employment of Bacillus bulgaricus, which is perhaps the best of the lactic-acid-producing organisms, as a means of preventing the growth of putrefactive organisms in the alimentary canal. To apply this treatment milk is sterilised and then inoculated with a reliable culture of the bacillus; it is kept warm until it is just curdled, in which stage many young and vigorous bacilli will be present. In the alimentary canal it is supposed that lactic acid will continue to be formed and that its presence will inhibit bacterial growth.

It has been used in various forms of gastric disturbance, in colitis, in auto-intoxication from intestinal putrefaction and similar conditions, but so far the treatment has not produced the beneficial results anticipated.

Tartaric Acid, $\begin{matrix}CH.OH.COOH\\|\\CH.OH.COOH\end{matrix}$

Tartaric acid is used with the soluble carbonates to make effervescing draughts: about 8 parts of the acid should be mixed with 7 parts of sodium bicarbonate for this purpose. Such drinks form a pleasant way of administering saline aperients. A small amount is absorbed and is excreted as carbonate in the urine, which is rendered more alkaline.

Citric Acid, $C_3H_4.OH.(COOH)_3$

Citric acid and lemon-juice are used as cooling drinks for febrile patients. Lime-juice and lemon-juice are prophylactics against scurvy, but this is not due to the citric acid they contain.

Citric acid, like oxalic acid, prevents clotting in freshly drawn blood, apparently by combining with the calcium. But calcium

citrate differs from oxalate in that it is slightly soluble. It forms the body $\begin{matrix}CH_2\cdot COO\\ CH\cdot OH\cdot COO\\ CH_2COO\cdot Na\end{matrix}\!\!\rangle Ca$, which does not ionise so as to liberate the Ca ion, and the specific action of citric acid depends upon its power of removing the calcium ions from the blood. Citrates are present in considerable quantities in human milk. A small proportion is absorbed and is excreted in the urine as carbonate.

Sulphurous Acid

The most characteristic property of this acid is its power of reduction. Thus, in the presence of water it tends to form sulphuric acid and to liberate hydrogen, $H_2SO_3 + H_2O = H_2SO_4 + H_2$. Sulphurous acid is, therefore, a powerful antiseptic and disinfectant, and acts by reduction. It is frequently used to disinfect rooms, and for this purpose sulphur is burnt in a moist atmosphere. Sufficient sulphur is however rarely employed, because for efficient disinfection from three to six pounds of sulphur should be used for every 1000 cubic feet of space; and the room must be kept closed up for about twenty hours.

Inhalation of the fumes of sulphur dioxide produces irritation of the mucous membrane. with sneezing, coughing, lachrymation, and bronchial catarrh. Sulphurous acid is sometimes used externally as an antiseptic in skin diseases.

Glycerophosphoric Acid; $\begin{matrix}CH_2.OH\\ CH.OH\\ CH_2.O.P\end{matrix}\!\!\begin{matrix}\diagup O\\ \diagdown OH\\ \diagdown OH\end{matrix}$

Glycerophosphoric acid and its salts were introduced into medicine because they are formed during the hydrolysis of lecithin. Now lecithin forms a large proportion of the solid matter of nerve-tissue, and it was hoped that the phosphorus in glycerophosphates might be built up directly into lecithin. No evidence exists that the glycerophosphates exert an action different from the ordinary inorganic phosphates.

MATERIA MEDICA

Acidum Sulphuricum.

Preparations

1. **Acidum Sulphuricum Dilutum.**—Contains 10 per cent. H_2SO_4.
   Dose, 5 to 20 m. (3 to 12 decimils).
2. **Acidum Sulphuricum Aromaticum.**—It contains much ethyl sulphuric acid.
   Dose, 5 to 20 m. (3 to 12 decimils).

Acidum Nitricum.

PREPARATIONS

1. Acidum Nitricum Dilutum.—10 per cent. HNO_3 by weight.
   Dose, 5 to 20 m. (3 to 12 decimils).
2. Acidum Nitro-hydrochloricum Dilutum.—Contains free chlorine.
   Dose, 5 to 20 m. (3 to 12 decimils).

Acidum Hydrochloricum.

PREPARATION

Acidum Hydrochloricum Dilutum.—10 per cent. of HCl.
Dose, 5 to 20 m. (3 to 12 decimils).

Acidum Phosphoricum Concentratum.

PREPARATION

Acidum Pnosphoricum Dilutum.—10 per cent. of acid.
Dose, 5 to 20 m. (3 to 12 decimils).

Acidum Aceticum.

PREPARATIONS

1. Acidum Aceticum Dilutum.—5 per cent. of acid.
   Dose, ½ to 1 dr. (2 to 4 mils).
2. Oxymel.—Honey with 1 in 10 acetic acid.
   Dose, 1 to 2 drs. (2 to 8 mils).

Acidum Aceticum Glaciale.—Should crystallise below 60° F.
Acidum Lacticum. Dose, 15 to 30 m. (1 to 2 mils).
Acidum Tartaricum. Dose, 5 to 20 grs. (3 to 12 dcgrms.).
Acidum Citricum. Dose, 5 to 20 grs. (3 to 12 dcgrms.).
Acidum Sulphurosum.—A solution corresponding to 5 per cent. SO_2.
Dose, ½ to 1 dr. (2 to 4 mils).

THE SOLUBLE ALKALIES

We include under this heading the carbonates, bicarbonates, and hydroxides of the metals potassium, sodium, and lithium. In the case of these salts the effect is due to the negative ion, that is, the OH ion, for the action of carbonates in the body is the result of dissociation, thus $NaHCO_3 = NaHO + CO_2$. The alkalinity is due likewise to the OH ion, and the hydroxides are, therefore, much more alkaline and exert a much greater toxic effect than the carbonates, as the latter only partly dissociate.

The carbonate and hydroxide of ammonia are not included in the group of alkalies, since their action depends rather on the liberation of free ammonia gas than on the presence of the OH ion.

All the alkalies possess certain properties in common. They neutralise acids, dissolve proteins forming alkali albumens, and saponify fats.

When a polybasic acid, such as phosphoric or carbonic acid, is partly neutralised by alkali, a point is reached when the solution

contains a mixture of acid and neutral salts which reacts approximately neutral to suitable indicators. To such a solution moderate additions of either acid or alkali may be made without changing the reaction of the solution, the only change being variations in the proportions of various salts. This mechanism is largely responsible for the maintenance of the essential neutrality of blood and other body fluids under changing conditions. A decrease in bicarbonate content may be present without increased acidity, provided that the respiratory centre is normally sensitive. The existence of this decrease implies production of fixed acid in the tissues (probably lactic acid), and this is due to deficient oxygenation.

Potassium hydrate, sodium hydrate, and lithium hydrate have a disinfectant action in proportion to their degree of dissociation, that is, to the degree of concentration of (OH) hydroxyl ions in the solution, and this affords some proof that it is the negative ions which produce these effects.

When these alkalies are applied externally to the skin they dissolve the superficial layers and saponify oily material, and are, therefore, used for cleansing purposes. They are employed in medicine to relieve irritation, such as from urticaria, nettle and insect stings, and this they do either by neutralising or removing the irritants. Strong solutions of the hydrates, which are much more corrosive than the carbonates, give rise to irritation, inflammation, and eventually to necrosis and ulceration. This "caustic" action is due to the affinity of the drug for water and to its power of dissolving albumen: when such caustics are used practically for the destruction of any superficial part, such as a wart, they are applied to the skin as a solid stick. Caustic potash is generally employed for this purpose, and, on account of its deliquescent properties and the severity of action, it is commonly mixed with lime and made into a paste with alcohol—Vienna paste.

Internal Action.—Alkalies possess a characteristic alkaline taste, and produce a soapy feeling in the mouth. They dissolve the mucus as well as the superficial layer of cells in the mouth, and inhibit the secretion of saliva so that the mucous membrane of the tongue and lips presents a bright red colour. Alkaline solutions may, therefore, be used to cleanse the mouth: they are also sometimes employed to give relief in toothache brought about by acid irritation in a decayed tooth.

On reaching the stomach they exert a very important effect. It should be remembered that water alone has some stimulating influence on the gastric glands; this is not a reflex effect through the centre, such as results from the action of food on the nerve-endings of taste, but a direct action on the glands, because section of the vagi does not prevent it. This must be kept in view when testing the action of other substances. Pawlow clearly showed that solutions of alkalies from 0.05 to 1 per cent. when placed in the stomach prevent this stimulating property of water, and he

also conclusively demonstrated that these drugs exert a decided inhibitory action on the gastric glands. These effects were shown by means of the artificial feeding experiments, already described under "Bitters," in which dogs were subjected to œsophagotomy, and also had a small portion of stomach isolated and attached to the skin for inspection. It was found that if animals received soda during feeding, this otherwise big juice-exciting procedure had very little effect, and that the pieces of flesh which dropped from the upper part of the œsophagus were scarcely insalivated. Now there can be no question that alkalies produce very beneficial effects in various derangements of digestion. These affections are commonly characterised in the earlier stages by a hypersecretion, in which there is a superfluous and useless flow of gastric juice. Later, it is usual to get a continuous secretion of slimy, weakly acid juice, and the gland-cells obtain no rest. The correct treatment in these cases would obviously be to give the stomach time for recuperation, to restrain this excessive work, and it is in this way that the alkalies are supposed to act. This treatment is analogous to the digitalis treatment of a very rapid heart. A dog whose stomach shows a well-defined artificially produced hypersecretion is also readily cured by alkalies: the secretion diminishes and the great excitement of the glands subsides.

Alkalies, such as sodium bicarbonate, especially when taken regularly for some time, diminish the flow of pancreatic juice. The cause of this is to be found in the diminished activity of the stomach. The secretion of hydrochloric acid is diminished and less secretin is formed in the duodenum, hence the flow of pancreatic juice is smaller than under normal conditions.

The secretion of bile does not appear to be altered.

Absorption.—The alkalies are absorbed as carbonate, and possibly to some extent combined with albumen. After absorption they necessarily increase the alkalinity of the tissues; for even when they are entirely neutralised by acid in the stomach, they will set free that alkali which would normally neutralise this acid during its absorption.

It is an old adage that any drug which increases the alkalinity of the tissues stimulates metabolism and increases the oxidation of proteins and fats. The reason given for this is that oxidation outside the body is generally more rapid in alkaline than acid solutions. The metabolic changes in the body are, however, not greater than can be accounted for by the simple salt action and diuresis. The urine shows a slight increase in the excretion of urea with a corresponding diminution in the excretion of ammonium. This may be explained by supposing that the acid absorbed from the alimentary canal is normally neutralised by combination with ammonium in the tissues, and that this is now replaced by fixed alkali; mineral acids should, therefore, increase the excretion of ammonia, which, as we have seen, is what occurs.

Respiratory Passages.—The carbonates check the mucous secretion of catarrh, but render what secretion there is more alkaline. They appear to act on these mucous glands in much the same way as they affect the gastric cells. The action is direct, through the circulation.

Urine.—Salt action is responsible for considerable diuresis, and the amount of all salts in the urine is found to be increased. The urine at first is rendered more alkaline from the bicarbonate excretion, but, unless large doses are taken frequently, it quickly regains its normal condition of acidity.

Action on Isolated Organs.—Small amounts of alkali increase the movements of leucocytes, amœbæ, cilia, and other forms of undifferentiated protoplasm, whilst larger amounts diminish the same automatic movements. Gaskell showed that dilute alkalies cause a tonic contraction of the muscle-fibre at the apex of the frog's heart: relaxation during diastole becomes less and less, and the heart ultimately stops in systole. Dilute alkalies also constrict the frog's vessels during perfusion. All these effects are antagonised by acids.

Effect of Alkalies on Uric Acid Excretion.—The important factor in the precipitation of free uric acid in the urinary passages is a strongly acid urine. Alkalies are used in medicine with the object of keeping uric acid in solution. They are of no value for dissolving uric acid already precipitated, but they form a means of arresting further precipitation.

The biurates of potassium and lithium are more soluble than that of sodium, therefore the former salts are used for preference in gout—a disease which is characterised by an excess of uric acid. Practically, however, it has been shown by Roberts, Luff, and others that alkalies cannot prevent or even delay the precipitation of sodium biurate from solutions of the quadriurate, which is the condition in which the uric acid exists in blood.

Alkalies produce no marked alteration in the excretion of uric acid.

MATERIA MEDICA

Liquor Potassæ.—5 per cent. solution. **Dose, 10 to 30 m.**

Potassa Caustica.—Must contain 85 per cent. KHO.

Potassii Carbonas.—K_2CO_3.

Potassii Bicarbonas.—$KHCO^3$. *See under* Potash Salts.

Sodii Carbonas.—Na_2CO_3. **Dose, 5 to 30 grs.** (3 to 20 degrms.).

Sodii Carbonas Exsiccatus.—Na_2CO_3. **Dose, 3 to 10 grs.** (2 to 6 degrms.).

Sodii Bicarbonas.—$NaHCO_3$. **Dose, 5 to 30 grs.** (3 to 20 degrms.).

Liquor Ammoniæ Fortis.

Liquor Ammoniæ.

Ammonii Carbonas.—$NH_4.HCO_3$ and $NH_4.NH_2CO_2$. A variable mixture. *See under* Ammonium Salts.

Lithii Carbonas.

Calx.

Calcii Hydras.—(CaH_2O_2). *See* Salts of Calcium.

CHAPTER XXIII

THE ACTION OF CERTAIN NEGATIVE IONS

Acetate, Nitrate, Sulphate, Phosphate, Tartrate, Citrate, Hypophosphite, Sulphite, Chlorate, Oxalate

Acetates, like chlorides, have no special action on the body: they are slightly decomposed in the stomach by the hydrochloric acid, and large quantities will produce a salt irritation. From the small intestine they are rapidly absorbed and are oxidised in the tissues to the carbonate, so rendering the blood more alkaline. Acetates are rapidly excreted as carbonate in the urine, increasing its alkalinity; only about 3 per cent. is excreted unchanged. They form excellent diuretics.

As acetates are oxidised in the body they must supply some energy, but they cannot be used to replace fats or carbohydrates like alcohol, because by exerting their salt-action they derange digestion and increase the urine.

NO_3 Ion.—Nitrates, though more or less foreign to the animal body, are nevertheless only slightly toxic, and lower forms of life and fish are hardly affected by dilute solutions of sodium nitrate. They induce salt action much like the Cl ion, but are more irritant, since an isotonic solution produces some irritation of the stomach and intestines. Hence, it is probable that there is a specific irritation besides the salt action. Big doses cause gastritis, nausea, vomiting, diarrhœa, and sometimes nephritis, and death occurs in much the same way as after big doses of sodium chloride.

Nitrates readily penetrate cells, and are easily absorbed. There is some doubt as to their excretion; part is undoubtedly excreted in the urine, and induces considerable diuresis; part by the sweat, which is also increased; and the drug is, therefore, said to be a diaphoretic. It has been supposed also that some of the nitrogen is given off by the lungs as gas.

Organic nitrates, such as nitroglycerin, are converted by organic matter into nitrites, but this action is negligible with the inorganic nitrates.

Bibulous paper soaked in a strong solution of potassium nitrate and dried, when burned slowly by allowing it to smoulder, gives off fumes which are inhaled to relieve the spasmodic constriction of the bronchioles in asthma. The effect is due to pyridine compounds.

SO_4 Ion. — Sulphates do not exert any specific action, and moreover they penetrate the tissues with difficulty, so that very little is absorbed from the alimentary canal. When introduced directly into the circulation sodium sulphate acts as a better diuretic than other salines, such as sodium chloride, possibly because it is not so readily absorbed by the renal tubules as the chloride, and thus retains a large amount of water. About one-tenth of the total excretion of sulphate is in the form of ethereal sulphate, derived from the aromatic substances in the food and from putrefaction in the bowel. Many aromatic substances are excreted combined with sulphuric acid, and so increase the ethereal sulphates in the body. Such substances are phenol, cresol, pyrocatechin, indol, and skatol. Sodium sulphate is used as an antidote in poisoning by phenol and some other aromatic bodies.

PO_4 Ion has no special effect. Phosphates given by the mouth exert a local cathartic salt action, and are only slightly absorbed. Injected subcutaneously some of the salt is excreted by the intestines and some by the urine. The normal phosphate in the urine is partly derived from food and partly from the nucleins of the cells.

Tartrate Ion.—Tartrates are not absorbed to any considerable extent from the alimentary canal, and they are, therefore, cathartic. Of the portion absorbed, one part is oxidised to the carbonate, and, being excreted by the urine, renders both it and the blood more alkaline ; the other part passes out in the urine unchanged. During excretion the flow of urine is increased by the salt action.

Citrate Ion.—Citrates behave much like the tartrates. They are not readily absorbed, and are, therefore, aperient. After absorption practically the whole of the salt is oxidised to the carbonate, in which form it is excreted in the urine. The soluble citrates are largely used to increase the flow of urine and to render the blood and urine more alkaline as in gout. When injected into man they retard the clotting power of the blood; this is due to the formation of calcium citrate, which, though soluble, presumably does not ionise.

PO_2 Ion (hypophosphites).—They are readily absorbed, and the whole can be recovered in the urine. It has been stated that they have an action on nutrition like phosphorus; they are, therefore, sometimes administered in wasting diseases such as phthisis. There is, however, no evidence to show that they behave differently from any other salts.

SO_3 Ion.—Sodium sulphite is a weak antiseptic, acting like sulphurous acid by reduction. It is given in 20-gr. doses to disinfect the stomach, especially when sarcinæ and torulæ are plentiful, and it is also used externally in parasitic skin diseases.

When sulphites are taken by the mouth sulphur dioxide is liberated in the stomach, and may induce nausea and vomiting. In poisonous doses there are restlessness and great muscular weak-

ness ; this is ultimately followed by respiratory paralysis and death. Injections of the drug under the skin are very much more poisonous and quickly induce paralysis of the medulla, including the vasomotor and respiratory centres.

Chlorates

The early writers on the chlorates supposed that they were reduced in the organism and gave up oxygen to the tissues. It is for this reason that they have come to be used so generally, both locally and internally, in foul conditions of the mouth and pharynx. But although they are not reduced to any extent in the blood and tissues of the healthy individual as formerly supposed—since from 90 to 95 per cent. of the salt can be recovered in the urine—they yet exert a beneficial effect in putrid inflammation of the mouth and throat, and in catarrh of the bladder with decomposition of the urine. The following is one explanation of the manner in which this is effected :—It is easily shown that chlorates undergo slow reduction when in contact with putrefying organic matter, and it is known that they are continuously eliminated by the salivary glands, the mucous membranes, and the kidneys ; hence, it is suggested that, although normal tissue fails to reduce them, the reduction is effected by septic tissue. The oxygen, being eliminated in the nascent state, would act as a mild irritant. Potassium chlorate is not more disinfectant than other salts, and is three or four thousand times less active than perchloride of mercury.

Action on the Blood.—Chlorates have a specific action on the blood. If sodium chlorate is added to a little drawn blood and shaken up, the mixture soon turns a chocolate colour, and shows the spectrum of methæmoglobin and, later, of hæmatin. In a short time the red blood-corpuscles are found to be partly disintegrated and the methæmoglobin set free in the serum. It will be remembered that the formation of the methæmoglobin by the nitrites does not involve this destruction of the red blood-corpuscles. The chlorate ion is not used up in the formation of methæmoglobin, so that an indefinite amount of this body can be formed from a small quantity of the drug—a further contrast to the nitrites.

Microscopical examination shows the red blood-corpuscles often misshapen and colourless, and the pigment in the form of round granules but retaining its colour. The diminution in the number of the corpuscles appears after the development of the brown coloration—that is, the methæmoglobin is produced before the destruction of the corpuscles. The disintegration is much more active in some animals, for example, the dog, than in others, such as the rabbit or man. The destruction of the colouring matter by chlorates is much slower than under the influence of acids or alkalies.

Taking man's blood as an example, the hæmoglobin is destroyed in the following times :

(1) Addition of 10 per cent. soda, one to two minutes.

(2) Addition of 10 per cent. acetic acid, eighteen minutes.

(3) Addition of 20 per cent. potassium chlorate, six hours.

Chlorates produce the same changes in circulating blood as on drawn blood. The formation of a small amount of methæmoglobin produces no evil results in animals, but when much is formed secondary effects arise from the disintegrated corpuscles, whilst a very large conversion prevents oxygenation of the blood and causes death from asphyxia.

Secondary effects of large doses of chlorates are mainly to be found in the kidney. The urine is dark brown in colour and contains albumen and hæmoglobin, as well as the products of the destruction of the red blood-corpuscles, which not infrequently occur in the form of casts. The disintegrated corpuscles may be present to such an extent in the blood as to block up the renal tubules and so lead to anuria and uræmia. Death from this cause would occur several days after taking the drug.

The bile pigment is increased, and jaundice sometimes ensues from its excessive absorption. *Débris* of red blood-corpuscles have been found in the liver, spleen, and bone-marrow.

Chlorates were once believed to have an action on the central nervous system, since intracerebral injections first excite and then paralyse the nerve-cells ; but sodium chloride will also produce this effect.

The chlorate ion is absorbed rapidly, and from 90 to 95 per cent. is excreted in the healthy individual, mostly by the urine, in which it may be detected about five minutes after administration, and in the saliva in the same time : the elimination continues for about forty-eight hours. The bronchial and nasal mucus, the perspiration, and the milk also contain the drug.

The *symptoms* seen after taking an overdose of the drug are, generally, nausea and vomiting arising from salt action, diuresis, cyanosis, heaviness and pain in the loins and abdomen, with brown and scanty urine. The cyanosis increases gradually, respiration becomes weaker, and death results from respiratory failure. The patient may continue to live for a week or more with gastro-intestinal symptoms, sometimes associated with jaundice and erythematous skin eruptions. In these cases the urine is at first scanty, brown, and contains albumen, casts, hæmoglobin, methæmoglobin, and hæmatin. Later the flow ceases entirely, and uræmia is the cause of death. Post-mortem, in these cases there is generally more or less inflammation to be found in the stomach, intestines, bladder, and kidneys, the tubules of the latter being plugged with blood-*débris*.

Oxalates

Oxalates act as general protoplasmic poisons; thus, they destroy low forms of animal life and algæ. If a little sodium oxalate is applied to a frog's nerve-muscle preparation, the nerve-endings are quickly paralysed and the nerve-fibres lose their irritability. The frog's and mammal's heart when perfused with sodium oxalate become gradually weaker, and ultimately cease to beat. It is conceivable that this effect is caused by precipitation of the calcium in the organism, and this is supported by the fact that moulds which are not influenced by oxalates contain no calcium, and also that calcium restores the lost function to a tissue which has been treated with oxalate. The latter is not very powerful evidence, as the calcium, before supplying the tissues, must first precipitate all the obnoxious oxalate.

Oxalates prevent the blood from coagulating whether they are injected into the circulation or added directly to the blood outside the body: they similarly prevent rennet from coagulating milk; in both cases they act by precipitating the calcium.

Oxalates are very irritant to the stomach and intestines, and when in concentration they may act as caustics like the mineral acids. They are absorbed slowly and are not oxidised to any extent in the body. When injected into animals, stimulation followed by paralysis of the central nervous system is produced, and respiratory failure causes death.

The prolonged administration of oxalates to rabbits has resulted in changes in the bone somewhat resembling those of rickets.

Excretion.—Oxalates are excreted in the urine, where they appear as the "envelope crystals" of calcium oxalate: these may be present in such large quantities as to block the urinary tubules and induce nephritis. Tomatoes, spinach, and rhubarb contain considerable quantities of oxalate, and it has been suggested that the salt may appear in the urine from the incomplete oxidation of carbohydrate food. Glycosuria and indicanuria are occasionally observed after large absorption of oxalates.

In cases of poisoning the treatment should consist in the administration of lime or any soluble calcium salt, together with considerable quantities of water, the object of the latter being to wash out from the urinary tubules the crystals of calcium oxalate.

MATERIA MEDICA

Potassii Acetas. Dose, 15 to 60 grs. (1 to 4 grms.).
Liquor Ammonii Acetatis. Dose, 2 to 6 drs. (8 to 24 mils).
Potassii Nitras. Dose, 5 to 20 grs. (3 to 12 decgrms.).
Potassii Sulphas. Dose 15 to 45 grs. (1 to 3 grms.).
Sodii Sulphas. Dose, 30 to 120 grs. (2 to 8 grms.) repeated, or to ½ oz. (16 grms.) single.

Sodii Sulphas Effervescens.—With sodium bicarbonate, citric acid, and tartaric acid. Dose, 60 to 120 grs. (4 to 8 grms.), or to ½ oz. (16 grms.) for a single administration.

Magnesii Sulphas. Dose, 30 grs. to 1 oz. (2 to 32 grms.).

Sodii Phosphas.—Na_2HPO_4. Dose, 30 to 120 grs. (2 to 8 grms.). ½ oz. may be given as a purgative.

Sodii Phosphas Effervescens.—With sodium bicarbonate, citric acid, and tartaric acid. Dose, 60 to 120 grs. (4 to 8 grms.), or up to ½ oz. for a single dose.

Sodii Phosphas Acidus.—NaH_2PO_4. Dose, 30 to 60 grs. (2 to 4 grms.).

Potassii Citras. Dose, 15 to 60 grs. (1 to 4 grms.).

Lithii Citras. Dose, 5 to 10 grs. (3 to 6 dcgrms.).

Lithii Citras Effervescens. Dose, 60 to 120 grs. (4 to 8 grms.).

Liquor Ammonii Citratis. Dose, 2 to 6 drs. (8 to 24 mils).

Potassii Tartras. Dose, 30 to 60 grs. (2 to 4 grms.) diuretic; 2 to 4 drs. (8 to 16 grms.) as a purgative.

Potassii Tartras Acidus.—$\begin{cases}CHOH.COOH \\ CHOH.COOK\end{cases}$. Dose, 15 to 60 grs. (1 to 4 grms.) diuretic; 2 to 8 drs. (8 to 32 grms.) as a purgative.

Sodii et Potassii Tartras.—$\begin{cases}CHOH.COONa \\ CHOH.COOK\end{cases}$. Dose, 2 to 4 drs. (8 to 16 grms.).

PREPARATION

Pulvis Sodæ Tartaratæ Effervescens.—Seidlitz powder. Sodium potassium tartrate, 120 grs., and sodium bicarbonate, 40 grs.; mix and wrap in blue paper. Tartaric acid, 38 grs., wrapped in white paper.

Sodii Citro-Tartras Effervescens. Dose, 60 to 120 grs. (4 to 8 grms.).

Sodii Hypophosphis.—$NaPH_2O_2$. Dose, 3 to 10 grs. (2 to 6 dcgrms.).

Calcii Hypophosphis.—$Ca(PH_2O_2)_2$. Dose, 3 to 10 grs. (2 to 6 dcgrms.).

Sodii Sulphis. Dose, 5 to 20 grs. (3 to 12 dcgrms.).

Potassii Chloras. Dose, 5 to 15 grs. (3 to 10 dcgrms.).

PREPARATION

Trochiscus Potassii Chloratis.—3 grs. in each.

CHAPTER XXIV

THE GROUP OF HALOGENS

IODINE

The element iodine is employed almost entirely as an external application, and it has been already considered in this connexion under "skin irritants." It is not often used internally, because potassium iodide has nearly all its properties without its disadvantages, such as gastric irritation. Its local action is in no way specific, and it differs from other local irritants only in that the action is slower in developing, milder in character, and more prolonged. Iodine dyes the skin a dark brown colour and precipitates proteids, with which it combines to form easily dissociated compounds; some diffuses into the deeper layers of the skin and becomes absorbed, so that, after painting the skin, iodides are always to be found in the urine.

The skin is inflamed and more sensitive: later, as the effect passes off, desquamation occurs. If a rabbit's skin is painted with tincture of iodine the diapedesis of leucocytes is easily observed, first in the subcutaneous cellular tissue, but later in the corium. The local changes produce certain general effects, which can be obtained by any local irritation; these are acceleration of the heart, rise in blood-pressure, and stimulation of respiration, besides reflexly influencing any organ which is supplied with sensory nerves from the same segment of the cord as the irritated skin under consideration.

When iodine is administered internally, it is absorbed as iodide and produces the usual effects of these bodies, being excreted in the ordinary way by the urine, milk, perspiration, and bronchial mucus; a small quantity is excreted as hydriodic acid into the stomach. It differs in its action from the iodides on account of its irritation of the stomach, large doses giving rise to gastro-enteritis and collapse: it is also believed to have a greater effect on the thyroid gland than the iodides, and symptoms of thyroid poisoning are said to be more common after its use. This statement, however, is open to doubt.

Solutions of iodine are sometimes used to wash out cysts in which putrefactive changes are going on, and the tincture is injected into the tunica vaginalis to excite adhesive inflammation and so produce a radical cure in hydrocele.

If free iodine is injected into the vein of an animal the pleuræ become inflamed and hæmorrhagic effusion with œdema of the lungs ensues; an effect almost similar to this may be obtained by injecting the iodides. Iodine is a valuable disinfectant and is often painted on the skin before operative incisions. It is better than most other disinfectants for this purpose on account of its penetration.

MATERIA MEDICA

Iodum.

Preparations

1. **Tinctura Iodi Fortis.**—10 per cent. of iodine.
2. **Tinctura Iodi Mitis.**—2½ per cent. of iodine.
   Dose, 2 to 5 m. (12 to 30 centimils).
3. **Unguentum Iodi.**—4 per cent. of iodine.

All these preparations contain potassium iodide, and the first two alcohol also.

IODIDES

The internal action of the iodides presents a remarkable similarity to that of iodine, and only differs in that the iodides are much less irritant to the stomach. Iodides have, therefore, come to be administered in almost all cases where formerly iodine was given. This resemblance between iodides and iodine naturally led pharmacologists to suppose that iodine was readily liberated from the iodide in the body, and that symptoms of "iodism" were due to the effect of the liberated element. That iodides are partly decomposed in the body one knows, because subcutaneous injections of potassium iodide into animals lead to some secretion of iodine into the stomach, and also because some of the iodine combines with the tissue-proteids, especially those of muscle, and forms an organic combination. Also, it is well known that iodides increase the amount of iodothyrin in the thyroid gland.

Iodism.—Iodides diffuse readily into cells and are very rapidly absorbed from the stomach and intestines: they can be detected in the saliva and urine a few minutes after a subcutaneous injection. In large amounts they produce the ordinary effects of salt action, as shown by irritation of the stomach and vomiting, and, after absorption, they often give rise to a remarkable series of symptoms known as iodism, a condition which can be obtained easily by the inhalation of iodine vapour. The generally accepted explanation of this condition is that during excretion some free iodine is liberated, and that iodism is the direct result of its irritant action. This condition begins with a brassy taste in the mouth and symptoms of an ordinary catarrh. Soon there appear an inflammation and swelling of the nasal, buccal, and respiratory mucous membranes. There is running from the nose, frontal headache due to extension to the frontal sinuses, and conjunctivitis,

since a trace of iodine is eliminated in the tears. The bronchial mucus is considerably increased, and the irritation of the iodine causes more or less cough; sometimes bronchitis is present, and in a few cases œdema of the lungs has been observed. The inflammation rarely affects the throat and larynx. If a large dose of sodium iodide is injected into a rabbit, no symptoms will be noticed for some hours; the animal then becomes ill and dies from œdema of the lungs and pleuritic effusion, due to local secretion of free iodine.

Iodide is eliminated partly by the skin and frequently gives rise to eruptions, most commonly acneiform, but almost any form of skin disease may be simulated: these are due to irritation of the sweat and sebaceous glands. Other effects of iodism are great depression, and increased metabolism leading to emaciation and sometimes to a kind of cachexia. In some cases iodides cause wasting of the mammæ and testes.

It is commonly stated that on increasing the dose of iodide the symptoms of iodism disappear, and such is undoubtedly sometimes the case; for example, patients who take 1 or 2 grs. with great inconvenience experience no ill effects when the dose is increased to 10 or 15 grs. Possibly the fact that iodine is freely soluble in potassium iodide may explain this, for by dissolving the free iodine it aids excretion.

Explanation of Action.—The question as to what causes the liberation of free iodine during the excretion of iodides from the body has been the subject of considerable discussion: as already observed, there can be no doubt that the conjunctivitis, coryza, and skin eruptions are produced in this way, and free iodine has been detected in some of the secretions. It has been suggested that the decomposition is effected by nitrites, ozone, carbonic acid, and other substances; but it should be remembered that iodides are very easily decomposed; sunlight, organic matter, and protoplasm will do this. Iodides enter into combination with the proteins of the body. This can be shown by injecting a little sodium iodide into a frog, when there is an almost immediate effect on the local muscles, which become hard, show an acid reaction, and enter into a sort of rigor mortis: the effect spreads slowly to the more distant muscles. This condition closely resembles that caused by caffeine. Free iodine cannot be detected in the muscles any more than it can be in iodoform; it exists in organic combination.

Action on the Thyroid Gland.—Most patients suffering from goitre—enlargement of the thyroid gland—improve under the influence of iodides, and the goitre becomes smaller. A few patients do not get well, but develop alarming symptoms. These consist of great and rapid emaciation, a very quick pulse, palpitation of the heart, tremors, nervousness, sleeplessness, headache, and atrophy of the breasts or testicles. These symptoms exactly

coincide with those of thyroid poisoning, and in no way resemble poisoning by iodides. In healthy people this condition is never produced, and a normal man may take enormous doses of the iodides without ill effect; but in those suffering from this peculiar disease of the thyroid the iodine produces a different result. Now we know that iodides increase the amount of one active constituent of the thyroid gland—the thyroxine—and this body produces symptoms similar to those described: it would, therefore, seem that in these cases there is a great deficiency of iodine in the gland, and that its sudden appearance sets free a quantity of very active secretion.

Simple goitre may be regarded as a compensatory hypertrophy, the result of a deficient internal secretion. The iodides diminish the size of the gland by increasing the activity of its secretion.

Other Actions of the Iodides.—The value of iodides in aneurysm is an established fact: and these remedies are also believed to produce beneficial effects in atheroma. The usual explanation of this has been that the drug lowers the blood-pressure either by depressing the heart or dilating the vessels; but iodides produce neither of these effects. It has been pointed out by Stockman that myxœdema (*see* Thyroid Gland) presents many similarities to premature senility, especially in the rapid development of atheroma, and so it has been suggested that a predisposing cause of both atheroma and aneurysm may be found in a failure of thyroid secretion. If this be so, the increased activity of the thyroid gland under the influence of iodides may lead to an absorption of the atheromatous tissue, such as occurs in myxœdema during feeding with thyroids. It is also claimed that iodides diminish the viscosity of the blood: if this is true it would afford an explanation of its action in arterial degenerations and aneurysm.

Iodides have a specific effect in syphilis, especially in later or tertiary syphilis, but until we know something more of the pathology of syphilis the way in which iodides act must remain uncertain. The absorption of growths in tertiary syphilis by the administration of iodides is generally regarded as due to liberation of iodine in the "gumma," a combination takes place between the iodine and the albumen, the cells die and are absorbed. In syphilis also some of the beneficial effects of iodides have been put down to augmented thyroid secretion.

Iodides are used in the treatment of poisoning by lead and mercury. They probably owe their efficacy here to their chemical property of being able to dissolve albuminous compounds of lead and mercury, and so facilitating their excretion by the kidneys.

Hydriodic acid has the general properties of iodides: it is best used in the form of the syrup when the salts of iodine disagree, and especially for children.

Elimination.—Iodides are rapidly excreted in the urine, saliva, perspiration, milk, and nasal mucus. After a hypodermic injection

of potassium iodide both free iodine and hydriodic acid can be detected in the stomach. It remains in the body a long time and is excreted very slowly, traces being found in the urine twenty to thirty days after the last dose. Metabolism is little altered. The excretion of nitrogen and sulphur is slightly increased, but the breakdown into urea and sulphates is not complete, and incompletely oxidised bodies appear in the urine.

Iodipin has been introduced as a substitute for iodides. It is a combination of iodine with unsaturated oils such as oil of sesame, and is frequently given subcutaneously, when it is slowly absorbed as iodide.

MATERIA MEDICA

1. **Potassii Iodidum. Dose, 5 to 20 grs.** (3 to 12 dcgrms.) or more.

PREPARATIONS

1. **Linimentum Potassii Iodidi cum Sapone.**
2. **Unguentum Potassii Iodidi.**—10 per cent.

Potassium iodide is used as a solvent in all pharmacopœial preparations of iodine.

2. **Sodii Iodidum. Dose, 5 to 20 grs.** (3 to 12 dcgrms.).
3. **Acidum Hydriodicum Dilutum.**—Contains 10 per cent. HI and 1 per cent. H_3PO_2. **Dose, 5 to 10 m.** (3 to 6 decimils).
4. **Syrupus Acidi Hydriodici. Dose, ½ to 1 dr.** (2 to 4 mils).

IODOFORM

Iodoform is principally used in surgery as a local application, and is commonly regarded as a valuable antiseptic. In the laboratory it has very little germicidal power; even a 50 per cent. solution does not kill most pathogenic bacteria such as staphylococci, although putrefactive microbes may be inhibited in their growth by quite small amounts; for example, it stops putrefaction of blood and retards the development of bacteria in bouillon. Its antiseptic properties are, however, too feeble to be of any practical use. How then does the drug produce its beneficial effects in wounds? Binz found that the emigration of leucocytes from the blood-vessels was hindered by the local application of iodoform, that is, the wounded surface secreted less; and some have relied on this for an explanation of its mode of action. Iodoform in the presence of putrefactive material, fat or ptomaines, is decomposed and iodine is set free. This nascent iodine rapidly enters into combination with any proteid material which may be present, and it is probable that this fact may account for some of the beneficial effects of the drug.

Iodoform, when taken into the body, is absorbed in two ways: a certain quantity passes into the system as iodoform directly,

but the greater part is decomposed by proteid solutions or alkaline fluids into iodides, and is so taken up. And as it has been already shown that the iodides increase the thyroid secretion into the blood, it is obvious that iodoform may cause a very complex set of symptoms, the result of (1) iodoform, (2) iodides, (3) thyroid secretion.

After long-continued doses, or where it has been slowly absorbed from wounded surfaces, a series of symptoms arise which bear a certain resemblance to those of alcohol or chloroform. They may come on gradually with general depression, headache, and a taste of iodoform; or develop suddenly, in which case there is usually some disturbance of digestion, vertigo, loquacity, and general want of self-control. Later, hallucinations and melancholia develop, and in some cases these are followed by violent mania. Ultimately death ensues from collapse. During the attack the temperature rises and the respiration and pulse are quickened; the heart in some cases is particularly accelerated, and it is believed that this acceleration is caused by thyroidism.

Frogs, dogs, and cats, after an injection of iodoform, show a general depression of the central nervous system with diminished reflexes. Post-mortem examination in these cases reveals fatty degeneration of the heart, liver, and kidneys. Besides these symptoms, all the effects of "iodism" may be seen, coryza and skin eruptions, &c.

Iodoform is excreted as iodide in the usual way, but after very big doses traces of iodoform can be found in most of the secretions. The iodine as usual is very slowly eliminated in the urine.

The disagreeable odour of iodoform has led to the introduction of a large number of substitutes, such as iodol  (tetra iodopyrrol), an odourless substance which, like iodoform, owes its action to the liberation of free iodine; aristol, a phenyl derivative, and loretin, a quinoline derivative, both of which contain iodine, and many others. The action of the latter two is due to their benzene nucleus and not to the iodine they contain, since no iodide is excreted in the urine: they therefore bear no pharmacological resemblance to iodoform.

MATERIA MEDICA

Iodoformum.—CHI_3. Dose, ½ to 3 grs. (3 to 20 ctgrms.).

Preparations

1. Suppositoria Iodoformi.—Iodoform, 3 grs. in each.
2. Unguentum Iodoformi.—1 in 10.

Non-official Substitutes for Iodoform

1. Iodol.
2. Aristol.—$(C_6H_2.CH_3.C_3H_7OI)_2$.
3. **Sozoiodolates of K, Na, Hg,** and **Zn.**—The acid = $C_5H_2\begin{cases}OH\\I_2\\SO_2OH\end{cases}$
4. **Loretin** is a derivative of quinoline.
5. **Iodine compounds of phenol-phthalein,** and many others.

It should be noted, however, that iodol is the only substitute in which the iodine is liberated in the body. The others have an entirely different action, in no way dependent on the presence of the iodine.

BROMIDES

These bodies exert a very definite pharmacological action, which is determined mainly by three factors:—(a) *Salt action,* (b) *a specific effect on the nerve-cells of the central nervous system,* (c) *the elimination of irritant substances during the excretion of the drug from the skin and mucous membranes.*

Bromides are soon absorbed from the stomach and intestines: they enter the blood as sodium bromide, and rapidly develop their specific action on the central nervous system. This begins with depression of the psychical functions, the motor area, and the medulla and cord, the last being shown by the diminished reflexes. The depression does not show an evolutionary progress as after alcohol. There is none of the uproariousness of the drunkard—the outcome of an over-activity of lower centres which have not yet succumbed to the poison—but, on the contrary, all the cells, psychical, motor area, medulla and cord, are affected at the same time.

The psychical condition is characterised by diminished intelligence, general mental apathy, confused thoughts and expressions, so that words and syllables are often misplaced. There seems to be a general dissolution of associations, giving rise especially to lapse of memory. The action on the cortex cerebri is much less defined in animals than in man; but the brain is much less developed in animals, and our means of testing it are very defective.

There is great diminution in the excitability of the motor area, and this is especially the case if the bromide is given for several weeks together. When dogs are thoroughly under the influence of the bromides, it is almost impossible to produce epileptic convulsions by cortical irritation. The drug blocks the passage of impulses along the paths which connect the motor centres.

The effects on the medulla and cord are shown by a general diminution of all reflexes. After a course of bromide the back of the throat may be freely swept round with the finger without inducing any effort to swallow or vomit, although the sensation

of touch is still present. Blunting of sensation and diminution of reflexes are also to be found in the conjunctiva, skin, and the mucous membrane of the genito-urinary tract, and the latter is responsible for the loss of sexual feeling.

Bromides, therefore, by lowering the activity of both motor and sensory cells, are invaluable in controlling the cortical explosions of epilepsy and in the treatment of cerebral excitement of all kinds. They promote sleep by rendering the brain less sensitive to disturbing influences. Some there are who assert that any good that bromides may do by controlling the fits is overshadowed by its harm. It is said to cause mental deterioration, loss of memory, and blunting of intellectual functions. On the other hand, these attributes, which are familiar enough in the chronic epileptic, are said to be secondary to the repression of the fits by "preventing the liberation of latent nerve energy."

Not infrequently, when the drug is administered over a long period, a series of untoward symptoms arise, which we speak of as "bromism." Bromism is probably due to irritation caused by the action of acid secretions on the bromides, whereby hydrobromic acid is formed, which may be decomposed with the liberation of free bromine. These consist of nausea and vomiting, produced partly by the salt action and partly by the liberation of free bromine and the excretion of hydrobromic acid into the stomach. An exaggeration of all the mental symptoms, such as sleepiness, mental dullness, and lapse of memory, is present. General muscular weakness and reduction of sensibility throughout the body cause an unsteady gait.

Various forms of skin eruption may ensue, acne, especially of the head and shoulders, being the commonest, and bromine has been detected in the pustule. These eruptions may be sometimes so severe as to form abscesses. Erythema and other rashes are occasionally present.

The buccal, nasal, and bronchial mucous membranes show signs of irritation. The breath is fœtid, the tongue foul, and the secretion of the nose and bronchioles is increased: sometimes there is cough and sometimes conjunctivitis.

Excretion is mainly in the urine; it begins soon after administration, but continues over a long period, often lasting two or three months, no doubt as the result of the bromine forming chemical combinations with the proteins of the body, which are very slowly destroyed. The urine is increased in amount and, besides bromides, contains a larger amount of chlorides. This is due partly to salt action, but also in some degree to the substitution of bromine for chlorine. Small quantities of bromide are also excreted by the skin, saliva, bronchial mucus, and fæces.

Bromipin is a combination of bromine with sesame oil. In the body alkaline bromides are liberated, but too slowly to render this drug of much value in the treatment of epilepsy.

MATERIA MEDICA

1. **Potassii Bromidum. Dose, 5 to 30 grs.** (3 to 20 dcgrms.).
2. **Sodii Bromidum. Dose, 5 to 30 grs.** (3 to 20 dcgrms.).
3. **Ammonii Bromidum. Dose, 5 to 30 grs.** (3 to 20 dcgrms.).
4. **Strontii Bromidum. Dose, 5 to 30 grs.** (3 to 20 dcgrms.).
5. **Acidum Hydrobromicum Dilutum.**—10 per cent. solution, HBr, in water. **Dose, 15 to 60 m.** (1 to 4 mils).

CHLORINE AND BROMINE

Chlorine and bromine have a similar action, but bromine is the more poisonous, because it is both volatile and fluid. They are very powerful disinfectants and deodorisers, and act through oxidation in the presence of water by virtue of their great affinity for hydrogen, thus :—

$$2Cl_2 + 2H_2O = 4HCl + O_2.$$

Their action may in part be explained by their replacing hydrogen in its combination with the proteids.

Chlorine is used as chlorinated lime to disinfect fæces, urinals, and drains. It is employed also to disinfect rooms after they have been occupied by patients suffering from infectious disease : for this purpose plenty of moisture should be present in the atmosphere. Disinfection by this body has the disadvantages that colouring matters are bleached and that clothing and metallic work are sometimes corroded.

Chlorine water is very irritant to the skin ; it produces redness and often painful blistering. Electrozone owes its antiseptic properties to chlorine ; it is prepared by the electrolysis of sea water, whereby hypochlorites are liberated. The inhalation of air containing chlorine causes irritation of the eyes, nose, larynx, and respiratory passages. Irritation of the fifth nerve may induce reflex effects—closure of the glottis, cardiac inhibition, and constriction of the bronchioles—all of which are protective, saving the animal from irritant particles or vapours entering with the air during respiration.

Chlorine is used as a gargle and mouth-wash ; for this purpose the mixture of chlorine and its oxides, which are liberated by the action of hydrochloric acid on potassium chlorate, is preferable to pure chlorine.

Commercial hypochlorite preparations commonly contain free alkali, and hence are irritating. A calcium hypochlorite and boric acid mixture has therefore been introduced under the name of "eusol." Dakin's solution of hypochlorite is also neutral, and a third contains a mixture of carbonate and bicarbonate. Such solutions are referred to as "buffer solutions," indicating their ability to reduce the change of reaction due to the addition of either

acid or alkali. The solvent action of hypochlorites on necrotic tissue is a great advantage when contrasted with the coagulating effect of many antiseptics on blood-serum and wound exudates. The hypochlorites, by virtue of their strong oxidising power, react readily with the toxic products of bacterial activity. The diminution in general toxæmia following the free use of hypochlorite in old, badly infected wounds, in which sterilisation is incapable of attainment, is a common observation.

MATERIA MEDICA

1. **Calx Chlorinata.**—($CaCl_2O_2.CaCl_2$.) Bleaching-powder.

PREPARATION

Liquor Calcis Chlorinatæ.—1 of chlorinated lime shaken up with 10 of water. It yields 3 per cent. of chlorine.

2. **Liquor Sodæ Chlorinatæ.**—(NaCl.NaClO.) **Dose, 10 to 20 m.** (6 to 12 decimils). As a gargle ½ dr. to an oz. of water should be used.

FLUORIDES

Fluorides have an extremely powerful local irritant action. Taken by the mouth they are absorbed in the merest traces only; they give rise to nausea and vomiting, and in large amounts entirely destroy the mucous membrane of the gut. If they are applied to the conjunctiva they produce violent congestion, destroy the superficial cells of the cornea, and produce opacities. Fluorides are general protoplasmic poisons and are powerful antiseptics, a 0.5 per cent. solution destroying most bacteria. When they are administered to animals in small amounts and over a long period, the bones become harder and more brittle than normal, and crystals of CaF_2 can be detected in them after death.

The injection of fluorides into the circulation of mammals causes convulsions of central origin: they are generally preceded by fibrillary tremors of the muscles, and followed by paralysis, coma, and death. The blood is prevented from clotting by the fixation of its calcium as calcium fluoride.

It has been suggested that the systemic action of the fluorides is produced in the same way as that of oxalic acid, to which it shows a marked resemblance, that is, by the formation of insoluble calcium salts. Fluorides are not used in therapeutics, though they are occasionally used as food preservatives; their employment for this purpose should be forbidden.

CHAPTER XXV

PHOSPHORUS, ARSENIC, ANTIMONY

PHOSPHORUS

Phosphorus is an element usually obtained from the calcium phosphate ($Ca_3P_2O_8$) of bone ash. It is an amorphous body and occurs in both yellow and red varieties. The former is much more volatile and soluble than the latter, and, as a consequence, it is easily absorbed from the alimentary canal. Red phosphorus, on the other hand, owing to its difficulty of absorption, is almost non-poisonous when taken by the mouth. The two varieties are equally toxic if injected under the skin.

The extensive use of phosphorus, both in the manufacture of matches and as a rat poison, is well known.

External Action.—In match factories the employés are sometimes subjected to the fumes of phosphorus. Here the direct local action of the drug upon the tissues exposed to the vapour can be observed. A common feature of such inhalation is irritation of the mucous membrane of the bronchioles, leading to catarrh. A more characteristic effect is necrosis of the lower jaw. This seems to be induced only when the periosteum is laid bare, such as occurs after the extraction of a tooth. Being thus exposed to the direct action of the fumes, the vitality of the periosteum becomes enfeebled, and so a nidus is produced suitable for the growth of organisms like the pyogenic cocci, and especially the tubercle bacillus. Thus, a tuberculous periostitis is induced, and in the later stages of "phossy jaw" the features of a tuberculous osteitis are present. This condition is more prevalent amongst those workers who are suffering from phthisis. In animals necrosis of the bone was never obtained by merely mixing phosphorus with their food.

Absorption.—The yellow variety is absorbed principally from the small intestine and circulates in the blood as phosphorus. Red phosphorus, we have already noted, is not absorbed on account of its physical properties. As the element is soluble in oily substances its absorption is considerably favoured by the presence of the oils and fats in the intestine, and it is also aided by the alkalinity of the duodenum. A small amount is converted into the gas PH_3. When viewed in the dark, the fæces of those taking the drug are phosphorescent.

Alimentary Canal.—Phosphorus is an irritant to the gastro-intestinal canal. Large doses produce flatulence, dyspepsia, vomiting, and colicky pains very quickly after administration. These effects are due to the direct irritant action of the drug on the mucous membrane, and must not be confounded with the alimentary symptoms which occur later in the history of the case, *i.e.* two or three days after the drug has been absorbed.

On the cytoplasm of the tissue-cells phosphorus exerts a profound influence, the results of which may be tabulated as follows :—

(1) *Deficient oxidation.*

(2) *Cloudy swelling, followed by shrinkage of the cytoplasm of the cells throughout the body.*

(3) *An increased breakdown of proteid, shown by the augmented excretion of nitrogen, sulphates, and phosphates in the urine.*

(4) *Diminution of glycogen in the tissues and an increased production of sarcolactic acid.*

(5) *The appearance of fat in the shrunken cells.*

Metabolism.—During phosphorus poisoning in animals the respiratory interchange (oxygen absorbed and carbonic acid eliminated) is diminished ; there is, however, some difference of opinion as to the reason of this. Some consider the altered gaseous exchange to be the direct cause of the deficient oxidation of the katabolites, while others regard it as a secondary effect, only occurring at a late stage in the poisoning.

The immediate cause of the diminished oxygen intake must be left undecided for the present.

In general starvation the body breaks up its own tissue to supply its immediate wants, and the same effect is seen in all forms of deficient nutrition. In phosphorus poisoning the increased excretion of nitrogen and of sulphates and phosphates must be due to increased proteid breakdown, and be correlated with the shrinkage of the cytoplasm of the cells, seen histologically. The output of urea may be increased or slightly diminished, but the increase, when present, is not at all proportional to the great increase of the nitrogen eliminated, which is often two or three times that of the normal. The ammonia excretion is greatly augmented. In the chapter dealing with acids it has been explained how, in man and the carnivora generally, any diminution in the alkalinity of the blood is met by an increase in the ammonia supplied by the tissues. Ammonium salts of the acid are produced, and the urea excretion may be diminished. The herbivora do not possess a like elasticity : in their case the fixed alkalies are used up to neutralise the acid, and since these alkalies are employed in the elimination of carbonic acid, death may ensue from carbonic acid narcosis. During phosphorus poisoning the ammonia of the urine is greatly increased in man and dog, but not in the rabbit : the administration of fixed alkalies, such as sodium carbonate,

to the former leads to a diminution of this excessive ammonia formation. The augmented nitrogenous elimination after phosphorus, therefore, appears to be due to an increased acidity of the blood. Lactic acid is the one present in great excess. Accordingly, the increased protein breakdown would seem to be a secondary effect due to lactic acid, a body which is apt to appear in any condition of imperfect oxidation.

By increased acidity or *acidosis* we mean a change in the physico-chemical equilibrium of the blood and a diminution in the alkali reserve, not a change in the reaction of the blood. The factors concerned in regulating the nice adjustment of the blood after such metabolic changes as these are: (1) The buffer salts, sodium bicarbonate; (2) the production of ammonium salts; (3) the hæmoglobin, which promotes the decomposition of carbonates if the hydrogen-ion concentration of the plasma tends to rise. (*See* Acids.)

This acid is probably at first derived from the incomplete combustion of the glycogen in the tissues, and, after this has been used up, from the tissue proteins themselves. Sarcolactic acid occurs as salts in the blood, and is excreted in the urine. A trace is said to be excreted from the stomach along with hydrochloric acid. It is generally assumed that the whole of the increased protein breakdown is due to the presence of lactic acid; but it should not be forgotten that deficient oxidation alone increases tissue waste.

The other nitrogenous bodies in the urine are but little affected; the elimination of uric acid is not altered; there is some increase of extractive substances, and there is also generally a small amount of certain other incompletely oxidised forms of nitrogen, such as leucin, tyrosin, and other aromatic bodies.

On the whole, then, the attention is drawn away from the nitrogenous breakdown, which appears to be secondary, and is centred about an abnormal oxidation of carbon compounds. There is the deficient carbonic acid elimination, the disappearance of glycogen, the excessive production of lactic acid, and, lastly, the deposition of fat in the cells.

The following is a simple way of connecting the facts:—

It may be supposed that in the normal katabolism of the protein molecule a nitrogenous portion is oxidised and excreted in the urine as urea, while a non-nitrogenous portion is burnt off as carbonic acid and water. It is this latter oxidation which is affected in phosphorus poisoning. As a consequence, there is a decrease in the formation of carbonic acid, and in its place an accumulation of fat appears in the cell, and such incompletely oxidised bodies as lactic acid are produced.

Certain syntheses performed by the cell are influenced by phosphorus. For example, when benzoic acid is perfused through the isolated kidney, the synthesis to hippuric acid is affected by the

cells; this process is inhibited by the previous administration of phosphorus.

Fatty Changes.—Whenever a drug causes an augmented breakdown of protein, fatty changes are apt to occur in the tissues. Such changes are induced after the administration of arsenic, antimony, phosphorus, benzol, alcohol, and the volatile oils. Moreover, it is found that there is deficient oxidation in association with these abnormal fatty changes.

The fatty change takes place in almost all tissues, and can be demonstrated in muscle (striped, plain, and cardiac), intestinal epithelium, kidney, and liver-cells. As the liver shows the change to a greater extent than other parts, it may be taken as the type for further consideration. In the early stages of chronic phosphorus poisoning it is usually enlarged and oily, and resembles the liver with fatty infiltration, which occurs after a period of acute alcoholism, or the liver which obtains in phthisis with general emaciation. The hepatic glycogen is diminished or absent; but this is more than balanced by the fact that the organ contains three or four times the normal amount of fat. The secretion of bile is at first increased, but as the liver-cells become distended with fat, and the canaliculi thereby compressed, jaundice sets in.

Much controversy has taken place as to whether the changes are to be regarded as a true degeneration of the material of the cell, that is to say, the fat is manufactured on the spot in the liver-cells, and is associated with the increased protein breakdown (Voit); or whether the fat is simply transported to the liver-cells from other parts of the body, and should be regarded as an index rather than the result of the cellular degeneration (Pflüger).

The fat cannot be that of the food, since phosphorus causes an increased amount of fat in the body even in starved animals. Nor can it be formed from glycogen, since all such reserves are used up very early in starvation.

Those in favour of the former of the two views mentioned above state that if a dog is starved until its tissues contain no fat, and if at this stage phosphorus is administered, the intake of oxygen and output of carbonic acid are diminished, while the output of nitrogen in the urine is much increased and fat appears in the cells. If this be true the fat must arise from proteid breakdown, although it may be either carried to the liver, being derived from the circulating proteid of the body; or it may be formed *in situ* from the degeneration of the cell-protoplasm itself. Further, if dogs are fed with a liberal supply of meat and a minimum of fat all this nitrogen is excreted as urea, but some of the carbon is retained. It is suggested that in phosphorus poisoning the proteid likewise splits up into a nitrogenous portion, which is oxidised and excreted in the urine, and into a non-nitrogenous portion, which is deposited in the tissues as fat.

Pflüger and others who adopt the second hypothesis do not

regard these observations as conclusive. They produce experiments to show that phosphorus does not increase the total fat present in the body, and also to show that fat may be transferred to the diseased cells. If a dog is starved till most of its fat has disappeared, and is then fed upon mutton suet and later poisoned with phosphorus, the usual fatty changes occur in the liver-cells, but this fat is not dog's fat, such as would be formed by the breakdown of the liver-cells, but is identical with mutton fat. In other words, the fat in the cells has been carried there from elsewhere.

According to this hypothesis, there is a general proteid shrinkage in the body with a concomitant general liberation of fat, and much of this is transported to the liver and deposited there. The fat which occurs in any particular cell is thus an index of the extent of its degeneration; the fat is not necessarily the result of this degeneration, as it may be formed elsewhere and deposited here.

A final decision between these conflicting views is at present impossible in the absence of sufficient experimental data.

Fatty "degeneration" is directly responsible for other symptoms in phosphorus poisoning. The epithelial cells of the stomach and intestines become swollen and cloudy, and later distinct droplets of fat appear in them. These changes explain the abdominal pain and vomiting, symptoms which are such common features in the secondary stage of the intoxication.

This fatty "degeneration" appears in all forms of muscular tissue: in striped muscle it causes muscular weakness and general debility; in cardiac muscle the change is quite decided and will be referred to later. Capillary hæmorrhages are not an uncommon feature in the second stage of phosphorus poisoning, and they appear to be due to degeneration of the intima of the vessels.

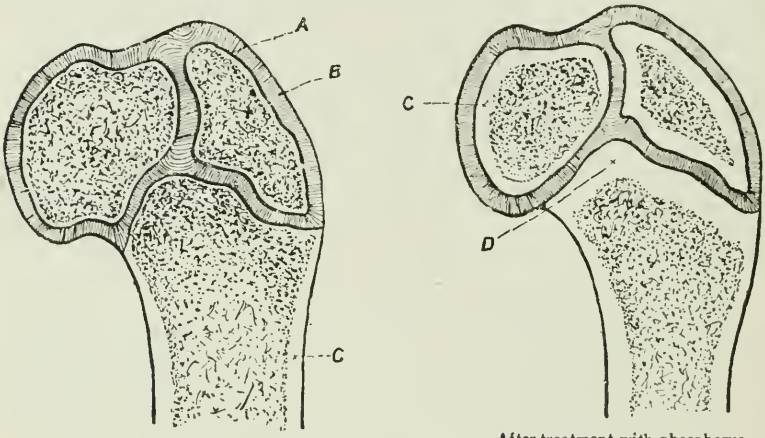
In the renal cells the change is indicated by the presence of albumen in the urine, sometimes with fatty casts, and in severe cases fatty globules are seen.

Bones.—Phosphorus is generally regarded as having a specific action on the bones whether formed in cartilage or deposited from the periosteum. If given to young growing animals the bones become denser than usual, and fresh tissue, which would be cancellous in the normal state, becomes compact, although the cancellous tissue which has been already formed remains unchanged. In all parts where spongy osseous tissue would normally be formed the exhibition of phosphorus induces a hard, firm, and uniform deposit of bone closely resembling that on the surface of the long bones. Fig. 84 represents a section of the humerus of a calf which had been taking small doses of phosphorus for eight weeks. It shows very clearly the layer of dense bone at the growing-point. If the administration of phosphorus be continued long enough, the cancellous tissue, which was formed previously to the administration of the drug, after a time becomes absorbed, and so one large medullary cavity is left. The flat bones deposited from the periosteum

undergo a somewhat similar change: they become thicker and denser, and the Haversian canals are in consequence diminished in diameter. All these changes in the bone are much more clearly seen in young than in adult animals.

If phosphorus is given to animals which have been previously starved of lime salts, like changes are brought about, except that the bone is now very deficient in calcium.

These facts suggest the therapeutic use of phosphorus in cases of bone fracture. It has been shown that if one of the limbs of an animal is fractured, the administration of phosphorus induces the injured periosteum to develop more and denser bone; and the callus, which is formed at the seat of fracture, becomes harder



Normal.

After treatment with phosphorus for eight weeks.

FIG. 84.—SECTION OF THE HUMERUS OF A CALF.

A = cartilage of the upper epiphysis. *B* = cancellous tissue. *C* = compact bone. *D* = dense mass of compact bone at the growing point (Wegner).

than usual and has an ivory-like appearance. Speaking generally, this drug should be employed whenever it is desired to excite the activity of the bone-forming tissues. Phosphorus has also been employed in the treatment of rickets and osteomalacia. It has been suggested that changes in the bone-marrow bring about these alterations in the bone. These changes closely resemble those produced by arsenic, and consist in a marked congestion and an increase in the number of the leucoblastic cells.

Moderate doses of phosphorus do not influence the number of the red corpuscles in the blood, but large doses lead to an excessive destruction of them, and it is possible that this setting free of pigment may account for the initial cholagogue effect in cases of poisoning.

Heart.—Small doses of phosphorus exert no action on the heart, and even in poisonous doses it is doubtful whether any effect is produced

until the third or fourth day, when degeneration of the cardiac muscle occurs accompanied by the deposition of fat. It is said that very large doses of phosphorus exert a specific action on the heart-muscle immediately after absorption, resulting in direct depression of the muscle and death from cardiac failure.

Excretion.—Phosphorus is oxidised in the body and excreted in the urine mainly as phosphates. Traces of phosphorus are excreted by the lungs.

Toxicology.—A large dose of phosphorus immediately gives rise to certain acute symptoms: they are burning in the mouth, throat, and stomach, followed by vomiting. Diarrhœa and colicky pains are occasionally present. These acute symptoms subside and the patient then appears to recover, except that there is, perhaps, a feeble pulse and some obscure pain. After two to five days the symptoms recur, the patient becomes dull and sleepless, complains of headache, and shows signs of jaundice. The liver is now enlarged and tender. The urine is dark and contains an excess of ammonia, some lactic acid, bile, albumen, and generally some leucin and tyrosin. The pulse is feeble and rapid. Sometimes the patient becomes delirious and passes into the typhoid state. Death ensues in about a week, although sometimes it may occur, much earlier and quite suddenly, from cardiac failure. In some cases twitchings, cramps, and convulsions are marked, and the fatal termination is preceded by somnolence and coma. In others, hæmorrhages occur from the skin, mucous membranes, and other parts of the body; and the vomit and fæces contain blood. Post-mortem the fatty change can be detected in the liver, kidneys, gastric mucous membrane, and cardiac muscle.

Poisoning by phosphorus can be readily recognised by the smell of garlic in the breath, by the phosphorescence of the vomit and fæces, which is best seen in the dark, and by the enlargement of the liver and the characteristic urine.

Treatment should first of all consist in emptying the stomach. This may be done by washing out with a 0.2 per cent. solution of potassium permanganate, as this converts the phosphorus into phosphoric acid and so renders it inactive. If the patient is seen early, emetics may be given; copper sulphate is the best, and 3 grs. may be administered in water every five minutes until vomiting is produced. Copper sulphate has a further advantage in that an insoluble copper phosphide is formed, and it may be that some of the metal is even precipitated upon the phosphorus globules, so retarding their absorption. Turpentine is used as an antidote in doses varying from 10 to 20 m., frequently repeated. This forms with phosphorus a solid body, terebinthino-phosphoric acid, which is non-poisonous. Mucilaginous drinks and alkalies may also be employed to neutralise the lactic acid. No oils or fats must be given, as they would aid absorption by dissolving the phosphorus.

In occupations in which phosphorus is used preventive measures

must be employed. Red phosphorus should be used whenever possible. Respirators are of some benefit, and the atmosphere may be impregnated with turpentine.

MATERIA MEDICA

Phosphorus. **Dose,** $\frac{1}{100}$ **to** $\frac{1}{25}$ **gr.** (0.6 to 2.5 mgrms.), best given in a pill made up with kaolin, or in solution.

Preparations

1. **Oleum Phosphoratum.**—1 per cent. solution in almond oil with 1 per cent. oil of lemon as a preservative.
   Dose, 1 to 5 m. (5 to 30 centimils).
2. **Pilula Phosphori.**—Containing 1 per cent. of phosphorus.
   Dose, 1 to 4 grs. (6 to 25 ctgrms.).

ARSENIC

Arsenic has an action in many ways resembling that of phosphorus. The metal is itself inactive: the pharmacological properties of "arsenic" are typically possessed by the negative ion $\overline{AsO_3}'''$ of arsenious acid (H_3AsO_3). Arsenious oxide (As_4O_6) is a powerful poison, which is but sparingly soluble in cold water; it is, however, readily converted by potash or soda into the more soluble arsenites. These possess the characteristic arsenical action, due to the arsenic ion formed by dissociation. Arsenic oxide and the corresponding salts are also poisonous.

The organic preparations of arsenic in which the element is directly combined with the carbon atom are relatively inactive. Thus, cacodylic acid $\left(HO.O.As\begin{matrix}.CH_3\\.CH_3\end{matrix}\right)$, which is a stable body, was for long considered quite inactive. There is no doubt that it possesses some slight toxic effect, quite out of proportion to the amount of arsenic present. It is probable that the poisonous action in this case arises after decomposition in the tissues, the odour of cacodyl, $As(CH_3)_2$, being distinctly evident. The ultimate change may be as follows:—

$$(CH_3)_2As.O.OH + 2H_2O = H_3AsO_4 + 2CH_4.$$

Similarly, the phenyl derivatives, although they do not contain the arsenic ion, are yet toxic in the body, since arsenic acid and benzene are formed.

$$\begin{matrix}C_6H_5\\C_6H_5\end{matrix}As.O.OH + 2H_2O = 2\,C_6H_6 + H_3AsO_4.$$

Diphenyl arsenic acid. Benzene. Arsenic acid.

Arsenical poisoning from wall-papers made with arsenic compounds is due to the formation of methylarsine, CH_3AsH_2, by the action of bacteria.

Action

External.—Arsenic, although an antiseptic, is much too poisonous to be employed for this purpose: it is used, however, in the dissecting-room to retard post-mortem decay. Most fermentations are but little influenced by its presence. Arsenic in dilute solutions is not absorbed from the unbroken skin; in strong solutions, however, absorption undoubtedly occurs. In those working with the metal it may collect in the crevices about the scrotum, gradually become dissolved in the secretions, and set up ulceration. Strong arsenical pastes were at one time employed to dress cancerous ulcers: they resulted in a dry gangrene, which ultimately separated as a slough. Poisoning occurred in a number of these cases.

Alimentary Canal.—Small doses of arsenic ($\frac{1}{60}$ to $\frac{1}{15}$ gr.) are said to increase the appetite and to promote digestion. In larger doses it is irritant to the whole gastro-intestinal canal. $\frac{1}{10}$ to $\frac{1}{2}$ gr. produces gastric pain, nausea, flatulence, vomiting, and diarrhœa. After 2 or 3 grs. all the alimentary symptoms are intensified, typical rice-water stools appear, and ultimately collapse and death occur; the condition closely resembles that of cholera. Post-mortem the mucous membrane of the stomach and intestine is red and swollen either in patches or uniformly distributed throughout; not uncommonly small hæmorrhages are also present. In some cases the stomach may be almost normal, but scattered red patches are generally to be found. Microscopical examination shows that in these patches the epithelial cells are frequently absent, they are easily rubbed away, and exhibit under the microscope the changes of cloudy swelling and, later, fatty degeneration: the interstitial tissue is filled with granular cells. The intestines contain a watery fluid mixed with the epithelial flakes. These changes are also produced when arsenic is injected under the skin.

In a general way these effects bear certain resemblances to those of the corrosive poisons, but, unlike them, the compounds of arsenic form no combination with proteids analogous to the albuminates of the heavy metals. Further, the action cannot be strictly local, since injections of arsenic induce the same result in the alimentary canal whilst producing little effect at the seat of injection: it is, however, necessary to give slightly larger doses subcutaneously to produce this action. A small proportion of the arsenic is excreted again into the intestines. Furthermore, corrosive poisons produce their effect immediately, while arsenic requires a definite latent period before its action becomes apparent. The action on the alimentary canal is not, therefore, a local corrosive effect, but a specific one, only produced after the absorption of the drug by the cells. The epithelium of the intestines degenerates and shows fatty changes, the vessels become widely dilated, and exudation into the connective tissue follows; this raises up the epithelium, which is thrown off in shreds, and the fluid is poured out into the

lumen of the intestines. The prolonged gastro-enteritis leads to exhaustion and death.

Metabolism.—Arsenic is used in therapeutics principally on account of its effect upon nutrition, which in certain abnormal conditions is considerably improved and fat is laid on. It is difficult to say how it brings about this effect, but it has been suggested that the cause may be its action on the alimentary canal, whereby appetite and digestion are improved. But arsenic has an action on the tissues very similar in kind to that of phosphorus but much less acute, and it would seem more probable that the improvement in the nutrition is due to these effects. These changes have been already tabulated under phosphorus; they consist of:—

(1) Increased protein breakdown, as shown by the augmented excretion of nitrogen (especially ammonia), sulphates, and phosphates in the urine. (2) Diminution of glycogen in the tissues, with an increase of lactic acid and a corresponding diminution in the alkalinity of the blood. (3) Fatty change affecting the liver, kidneys, heart, and muscles generally.

These changes are supposed to result from diminished oxidation of the tissues induced by the direct action of the drug on the cytoplasm of the cells. Binz explains the action of arsenic by supposing that the arsenious acid is oxidised in the tissues to arsenic acid, and that arsenic acid may be converted again into arsenious, so that arsenic is employed by the body as an oxygen-carrier. This very speculative hypothesis cannot be considered in harmony with the evidence.

Upon the growth of young animals the influence of arsenic resembles that of phosphorus: growth is more rapid, the animals attain a larger size, and the bone-forming tissues appear to have greater activity. After the absorption of the drug for some weeks the long bones present the appearance described under Phosphorus, the cancellous bone being replaced by compact tissue.

If small doses of arsenic are administered to animals the red bone-marrow becomes hyperæmic, the fat-cells disappear, and there is a decided increase in the number of leucoblastic cells (Fig. 85). It is generally assumed that arsenic increases the formation of red blood-corpuscles since it acts beneficially in pernicious anæmia, a disease in which these corpuscles are very deficient owing to excessive destruction; this assumption obtains no support from experiment, since the erythroblasts of the bone-marrow are not increased. The rapid growth of the bones may be secondary to the increased vascularity of the marrow.

When the administration of arsenic is pushed severe anæmia often results, which is coincident with the ultimate degeneration of the bone-marrow. Now, arsenic produces a very beneficial effect in pernicious anæmia, and, as it does not act by stimulating the marrow to form fresh cells, Stockman has suggested that it may have a specific effect on some parasite.

Nervous System.—Arsenic has no important action on the

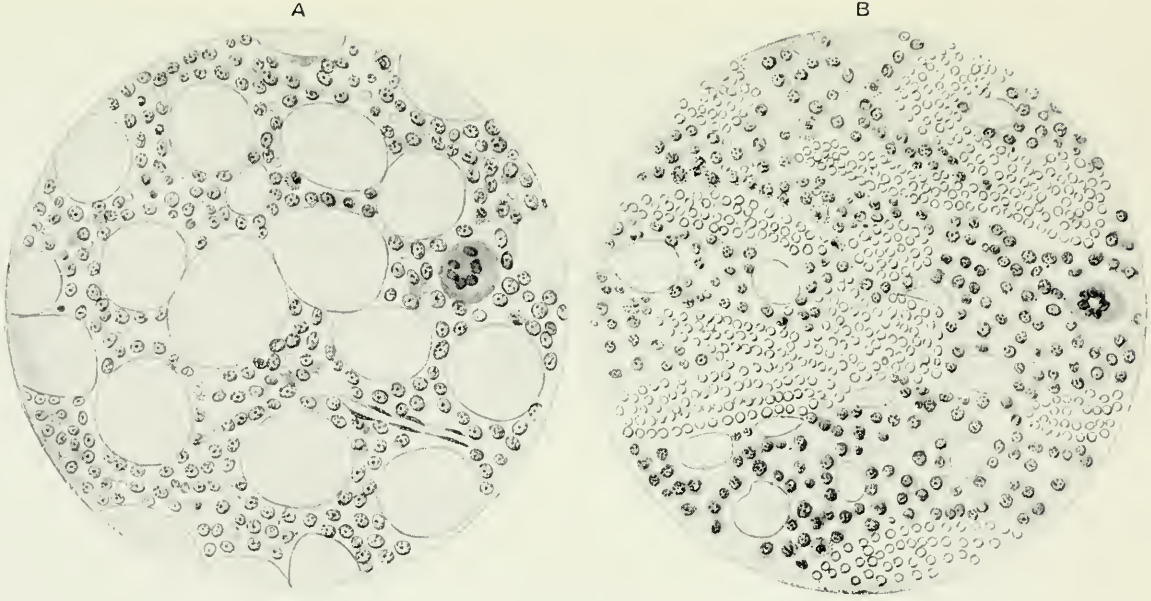


FIG. 85.—BONE-MARROW FROM THE UPPER END OF THE FEMUR OF A YOUNG RABBIT.

A = normal bone-marrow. It shows numerous large fat-cells, a myelocyte on the right, marrow-cells, eosinophil-cells, and some red blood-corpuscles.

B = bone-marrow after the administration of arsenic for sixty days. It shows the blood-vessels greatly increased and filled with corpuscles, the fat-cells few and atrophied and the marrow-cells increased in number, the increase being in the leucoblastic, not in the erythroblastic cells. Further administration of arsenic produces hyaline degeneration in the marrow.

It should be particularly noted that these changes are not peculiar to arsenic, but occur with many other bodies (Stockman).

To face p. 376

central nervous system. It is true that when administered to frogs it produces paralysis of the brain and cord, but in mammals death occurs from collapse, induced by the gastro-enteritis, long before any such effect is patent.

Under certain conditions it gives rise to a peripheral neuritis, which closely resembles that of alcohol. The action is essentially one on the interstitial tissue, the connective-tissue sheath of the nerve being affected in the same way as connective tissue elsewhere in the body. It becomes hyperæmic, shows multiplication of new tissue elements, and migration of leucocytes. These changes lead to pressure on the nerve-fibres, and so to their degeneration. The effect is generally symmetrical; the extensors of the foot, the interossei and opponens pollicis of the hand are first affected. The symptoms will be described under Toxicology.

Circulation.—In some cases of chronic poisoning failure of the heart's action has been observed; it shows itself in œdema of the feet and legs and a feeble pulse of low tension. Probably this is due to degenerative changes in the muscle analogous to those occurring in phosphorus poisoning. Therapeutic doses of arsenic do not directly influence either the heart or respiration.

Skin.—In man arsenic has a beneficial effect upon the nutrition of the skin, the subcutaneous fat is increased and the complexion is improved; also, it renders the coat of certain domestic animals, as the horse, thicker and more glossy. How this beneficial effect is brought about we cannot say with certainty. Apparently, it is not due to increased blood-supply from local vaso-dilatation, nor is there evidence that it is a nervous effect. There are, however, two other factors to consider:—(1) Arsenic may have a specific action upon cutaneous epithelium during its excretion; and (2) it may increase the flow of lymph to the part.

In support of the former hypothesis there is definite evidence that arsenic is to some extent excreted by the skin. It can be found in the epithelial cells and hair of animals that are taking the drug, and has been detected in the blister-fluid of a patient under treatment with arsenic. If arsenic is given to frogs, the epithelial cells soften and shrink, and the skin readily peels off.

The latter hypothesis, that arsenic may act as a lymphagogue, has received no attention as yet. Sometimes the stimulant action of the arsenic leads to hyper-activity of the skin, as shown by an overgrowth of the epithelium (keratosis) and papular, vesicular, or scaly eruptions; and it has been stated that the prolonged use of arsenic may give rise to epithelial cancer.

The most characteristic action on the skin is the brown coloration of the face and other parts of the body (melanosis). It has been seen already that poisonous doses of arsenic cause an increased destruction of the red corpuscles, and the pigmentation may be due to hæmoglobin derivatives obtained from these corpuscles.

The irritation of the mucous membranes of the eyelids, nose,

pharynx and trachea, and alimentary canal is probably the result of conditions similar to those obtaining in the skin.

Tolerance.—The system may be cultivated to withstand large doses of arsenic without showing the usual physiological effects. If an animal is given a daily dose of arsenic, beginning with a very small one and gradually increasing, after some months many times the lethal dose may be taken without any symptoms of poisoning. A like toleration can be induced in man. The Styrian peasants of a certain class at one time took the drug to increase their powers of endurance and to improve their wind when climbing. In some cases it was also said to be taken to render immune those employed in arsenical works or in the working of ores containing arsenic. These people for the first week or so took a dose of arsenious acid varying from $\frac{1}{20}$ to $\frac{1}{8}$ gr.; this was followed by a period of abstinence. Afterwards they again took the drug, but in increased doses, and this alternation was continued until 6 or 7 grs. could be taken at one dose. Attempts to produce tolerance to arsenic in this country have not been very successful.

It is difficult to explain this form of immunity. It is not always due to less rapid absorption or more rapid excretion, since these processes may go on normally, and considerable amounts of arsenic have been extracted from the urine. It has been suggested that an antitoxin is formed, and in support of this is the fact that the subcutaneous injection of serum from tolerant animals will prevent death in normal animals which have received a fatal dose of arsenic. Such an immunity is very limited, for should the amount of arsenic slightly exceed the minimal fatal dose, death always occurs.

It has been demonstrated that a dose of arsenic which is fatal subcutaneously can be injected into a peritoneal cavity without causing death. Here a number of leucocytes are available, by which the arsenic is absorbed; it has been suggested that they convert it into a non-toxic compound, and, later, excrete it.

Tolerance to arsenic may be acquired by protozoa, such as the spirochætes of relapsing fever and trypanosomes. It is well known that Ehrlich gradually produced atoxyl-fast strains of trypanosomes which when injected into mice produced a trypanosomiasis which atoxyl even in the largest doses failed to influence. These particular trypanosomes *in vivo* are uninfluenced by arsenical preparations, but *in vitro* they may be even less resistant than ordinary trypanosomes. One interpretation of this fact is that this breed of hypersensitive trypanosomes can pick up a shield from the organism on which they are parasitic as a means of protecting themselves from arsenic, and one such shield might well be a chemical substance of such a nature that a combination occurred between it and the arsenic whereby a non-ionisable arsenical compound was produced, in exactly the same way as salicylic acid is rendered non-poisonous by combining with glycocoll. Or we might imagine that this breed

of trypanosomes contains a relatively large amount of a ferment facilitating the combination of an organic substance contained in the blood with arsenic.

Cloetta found that dogs could receive by the mouth gradually increasing doses of arsenious acid without poisonous symptoms arising, but that if the administration by the mouth be stopped and a dose of the drug much smaller than the dose given by the mouth be injected subcutaneously grave symptoms of poisoning set in and the animal dies. It cannot therefore be said that a patient has been really accustomed to arsenic because he has been able to support gradually increasing doses of the drug administered by the mouth.

Excretion.—Arsenic is mainly excreted in the urine as inorganic compounds, but the excretion is slow, and traces are often found two or three weeks after the administration of the drug has ceased. A small percentage is also excreted by the stomach, intestines, and milk, and poisonous symptoms have occurred in infants where the mother has been taking the drug. If an animal is killed after absorbing arsenic the organ which contains the greatest percentage of the drug is the liver ; then come the walls of the alimentary canal, the spleen, cancellous bones and hairs, which all contain a small quantity.

Toxicology.—The administration of a large dose of this drug produces symptoms which are principally the result of the specific action of the drug on the alimentary canal. We have pointed out already that arsenic is not a corrosive poison like the salts of many of the heavy metals, because the effects of the drug are not observed for at least half an hour after it is administered. They then commence with severe abdominal pain, associated with nausea and vomiting. The vomited material consists of the contents of the stomach mixed with regurgitated bile, to which are added, later, streaks of blood. The epigastrium is very tender and vomiting gives no relief.

The most characteristic feature of this type of poisoning is diarrhœa, which resembles that of cholera. It is painful and profuse : at first there is nothing special to note, but soon the straining (tenesmus) becomes very distressing and the stools assume the form known as "rice water." They consist of shreds of disintegrated mucous membrane floating in a serous fluid which, in the later stages, is mixed with blood.

The withdrawal of water by the stools leads to thirst, dryness of the mouth and throat, and difficulty in swallowing. The urine also is much diminished, and in severe cases contains albumen and blood, the latter signs being due to a nephritis induced by the arsenic during its excretion by the kidneys. As in cholera, there are severe muscular cramps, headache, giddiness, and prostration.

The patient becomes more and more prostrate and feeble. The

circulation shows signs of failure, the pulse being of very low tension, weak and irregular. Temperature falls gradually till considerably below the normal, the skin being cyanosed and covered with a cold and clammy sweat. The collapse ends in death, which occurs eight hours to three days after the administration of the drug. Nervous symptoms do not, as a rule, precede death, but epileptiform convulsions, and sometimes paralysis and coma, have been observed.

Not infrequently the patient recovers from the acute symptoms, but develops subsequently the symptoms of a chronic intoxication. Chronic poisoning may follow the therapeutic administration of arsenic, but it occurs more commonly in connexion with occupations where some compound of arsenic is employed. The symptoms consist of :—

(1) *Irritation of the mucous membranes of the eye, nose, throat and larynx.*
(2) *Alimentary symptoms.*
(3) *Peripheral neuritis.*
(4) *Skin eruptions.*

In the mild cases the effect on the eyes is particularly characteristic. There is considerable irritation, redness, and swelling of the conjunctiva ; the eyelids, especially the lower one, are œdematous and the patient is intolerant to light. The mucous membranes of the nose, pharynx, and trachea are inflamed, the tracheitis giving rise to a short dry cough. Alimentary symptoms are not pronounced in mild cases, but there is loss of appetite with irregular attacks of nausea and vomiting without any apparent cause ; more occasionally there is diarrhœa. Skin eruptions of a trifling nature may appear, and occasionally some signs of peripheral neuritis. All these symptoms may result from the administration of large but medicinal doses of arsenic ; they are seldom serious, and disappear when the dose is diminished.

In the more severe cases of chronic poisoning, such as occur in the textile arts, both the digestive symptoms and the irritation of the other mucous membranes are more pronounced, so that it is not uncommon to find bronchitis and laryngeal catarrh. The most characteristic features, however, are affections of the peripheral nerves and eruptions of the skin.

The peripheral neuritis bears a close resemblance to that of alcohol : there is a feeling of coldness, numbness, and tingling in the hands and feet, often accompanied by a creeping sensation, which may at times be positively painful. Areas of anæsthesia to touch and temperature in some parts, and areas of hyperæsthesia in others, complete the sensory symptoms. The motor symptoms consist of either simple muscular weakness or complete paralysis of the extensor muscles of the forearm and leg, causing "wrist drop" and "foot drop." The gait is consequently ataxic and the knee-jerks commonly absent. In severe cases there is considerable atrophy of the muscles, which show the reaction of degeneration.

These symptoms, being due to a general condition, are necessarily symmetrical.

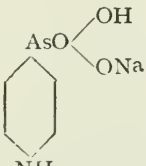
Skin eruptions are very characteristic of arsenical poisoning. We have already seen that the drug has a stimulant action upon the skin, and this would seem sometimes to be exaggerated and result in rashes, such as keratoses of the hands and feet, while the hair and nails become dry and brittle. Erythematous eruptions resembling measles, scarlatina, or eczema are sometimes found; they are irritable and often succeeded by scaly desquamation. Herpes and other eruptions may be due to trophic changes brought about by the peripheral neuritis. But the most characteristic skin affection is the bronzing that sometimes affects the whole body, but more commonly occurs in patches. The pigmentation is always marked at points of pressure, and is particularly well seen in the armpits and nipples. Recovery is usually very tedious.

The trades in which arsenical poisoning is apt to occur are those concerned in the manufacture of arsenical pigments (especially green), wall-papers, coloured cardboard boxes, and artificial flowers; paperhangers and decorators may also be affected. Arsenic, being volatile, is liable to cause poisoning in any trade in which it is employed. Metal-workers in zinc and brass are particularly subject to this, owing to the arsenical fumes evolved from the heated metal.

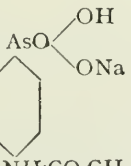
The diagnosis of arsenical poisoning is not, as a rule, difficult: in the more acute cases the sudden onset and persistence of the symptoms distinguish it from an ordinary bilious attack.

Treatment should consist, in the first place, in getting rid of any arsenic which may still be present in the system; this is done by washing out the stomach with warm water. Afterwards, large doses of freshly prepared hydrated peroxide of iron should be given; it can be made by adding powdered magnesia to a solution of ferric sulphate.

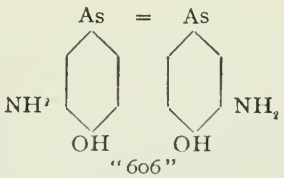
A number of *organic compounds* of arsenic have been introduced into medicine for the destruction of protozoa, especially in the treatment of trypanosomiasis, syphilis, malaria, and pernicious anæmia.



Atoxyl.



Arsacetin
(acetyl atoxyl).



"606"
dihydroxy-diamino-
arsenobenzene
(salvarsan).

These bodies contain no ionic arsenic, so they are without action on protozoa *in vitro*, but in the body they are much more efficient in the destruction of protozoa than an equivalent amount of arsenious acid. Possibly the parasites or the products of their metabolism may

break down these bodies and liberate the arsenic in ionic form in concentration in their neighbourhood, thus bringing about their own destruction.

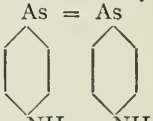
Atoxyl is soluble 1 in 5 water. It is somewhat unstable and the solutions cannot be boiled; it is stated to have only one-fortieth the toxicity of arsenious acid.

Organic arsenical compounds, like atoxyl and salvarsan, have an advantage over inorganic arsenic compounds, in that they are absorbed more readily into the colloids of the cell. If such a substance is injected into the vein of an animal, arsenic can be found in the blood plasma and corpuscles in a form which cannot be removed by dialysis, but which is precipitated with the serum proteins by tannic acid. The organic arsenic compounds for the most part form colloidal solutions which readily mix with proteins.

Taken internally, most of the atoxyl passes through the body unchanged, but a small portion becomes changed, and this portion can apparently destroy most of the parasites (trypanosomes or spirochætes) in an infected animal.

It may be taken as an axiom that substances containing arsenic in the trivalent form are much more toxic and efficient in destroying parasites than the corresponding compounds with pentavalent arsenic. A glance at the formula for atoxyl will show that the arsenic here is pentavalent. If this body is reduced, as we believe some of it is in the body,

is formed, which by further reduction becomes

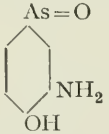


These, being trivalent, are both much more toxic and poisonous to protozoa, which they kill *in vitro*.

Atoxyl then appears to act first by its ready penetration of the cell and then by its slow reduction into the more active trivalent condition. It is interesting to note that the entrance of a sulphonic acid group into the molecule produces a substance which is without toxicity. Dose, up to 15 grs.

Arsacetin is more stable than atoxyl and its solutions can be boiled; it is also less toxic. Dose, up to 15 grs.

Arsenobenzol "606" or *Salvarsan* is also soluble in water. Like atoxyl it is not directly toxic to parasites; it circulates in the blood in a colloidal form protected from aggregation by the plasma proteins, and is quickly deposited in the tissues. The arsenic is in the pentavalent form, but in the tissues it appears to be partly oxidised into the trivalent form,



The addition of liver emulsion to arsenobenzol gives to it the power of killing spirochætes even *in vitro*, so that the arsenic must have been converted into the trivalent form, and the new body is probably that shown in the formula. This substance is stable and easy to administer, and when injected into animals infected with spirochætes or trypanosomes causes these parasites rapidly to disappear from the blood; but the action is evanescent and relapse is quick. Arsenobenzol is more efficient because its oxidation into a trivalent substance is slow, so that a steady supply of efficient parasiticide is thrown into the blood. It will thus be seen that the action of arsenobenzol is on the organism and only indirectly on the parasite. Dose, up to 12 grs.

Novarsenobenzol (Neo-salvarsan) has been introduced to replace salvarsan, as it is less toxic and believed to be equally efficient: its solubilities are also more favourable for administration. The arsenic content of three parts of novarsenobenzol is roughly equivalent to two parts of arsenobenzol. This substance is obtained by replacing one atom of hydrogen in one amino group of arsenobenzol by the group (CH_2OSONa). It is not a pure chemical substance but is mixed with inert inorganic salts.

The best method of administering these drugs in syphilis is by intravenous injection when there is a rapid disappearance of parasites from the blood. The organic arsenical preparations have affinities for special tissues. Thus, after administration to animals, atoxyl and arsacetin can be detected in the eyes, but inorganic arsenic and salvarsan cannot be so detected; this is the explanation of the optic neuritis and blindness which have brought about the disuse of the two former. Again, after administering salvarsan to a rabbit with syphilitic corneal ulceration, arsenic can be detected in the cornea but in no other portion of the eye.

The conversion of these compounds into the active trivalent form occasionally leads to poisoning. This may be of two kinds:—(1) Symptoms of acute arsenical poisoning which have been considered already; (2) toxæmia. In these cases of delayed poisoning the symptoms occur usually after the completion of a course of treatment, and when a full amount of the drug has been administered; but they may be seen during treatment and after the injection of one or two small doses. The symptoms and signs correspond closely with those of delayed chloroform poisoning or with phosphorus poisoning, and are characterised by jaundice, hæmorrhages, delirium, and coma. In most people we know that arsenobenzol is slowly converted into active arsenic, but we cannot explain why some people can effect this change rapidly (acute poisoning), or why others store the drug in their tissues, it may be for weeks, when the conversion comes about in an explosive fashion (*cp.* sulphonal poisoning). This is the usual form in which death may occur: arsenic can be found in the abdominal viscera but not in the nervous system.

ANTIMONY

Antimony is the last member of this group, and stands, as regards its action, midway between arsenic and the heavy metals. The main difference between it and arsenic depends upon the facts that (1) it is absorbed with difficulty, and (2) it is more irritant to the alimentary canal. It is possible that the fact of its not being readily absorbed depends upon physical properties: in support of this we notice that the elements phosphorus, arsenic, and antimony are absorbed from the alimentary canal just in proportion as they are volatile; and, further, the only heavy metal which is absorbed at all readily is mercury, and this is also the only one of these metals which is volatile.

The tartrate of antimony (tartar emetic) (SbOKT) is the salt generally employed in medicine, chiefly on account of its easy solubility, cheapness, and activity.

Antimony, like arsenic, has an irritant action on all epithelial cells.

Externally it acts on the skin as a severe irritant, and produces round the sweat and sebaceous glands papules and pustules which

resemble the pocks in small-pox. As a counter-irritant it is useless because it is uncertain, and the pustules, which may be formed after a few days, sometimes coalesce and produce a bad scar, or even local necrosis.

Certain salts of antimony, like the chloride, are caustic, and differ from tartar emetic by combining with albumen in the same way as the heavy metals.

Internally tartar emetic in small doses (½ gr.) gives rise to nausea, and in larger doses (2 grs.) to violent vomiting. The vomiting occurs from seven to twenty minutes after taking the drug and, as in vomiting from other causes, is associated with certain effects, all of which are induced reflexly through the medulla. Respiration becomes quicker and deeper, and the flow of saliva and bronchial mucus greater; the pulse-rate is increased—an effect which is usual after any mild form of peripheral irritation, such, for example, as a blister. The face is flushed, but the limbs suggest a sensation of cold and are covered with perspiration. It has already been seen that stimulation of the medulla, either directly or indirectly, induces constriction of the splanchnic area and dilatation of the skin-vessels.

The emesis after antimony is due to a direct irritant action on the stomach. If the drug is injected subcutaneously vomiting is still induced, in which case not only are larger amounts required but it takes longer to act. This forms a conclusive proof of its peripheral action, and there is no reason to suppose that it has a direct action on the vomiting centre. Any irritant substance, including antimony, when injected subcutaneously, induces vomiting, generally by irritation of some portion of the alimentary canal. It is also well known that any form of peripheral irritation, provided it is sufficiently severe, produces the same effect; thus, a moving stone in the gall-bladder or in the pelvis of the kidney will produce vomiting; or, again, the stimulation of the central end of an afferent nerve, such as the vagus or glossopharyngeal, will also cause the same effect. The experiments of Majendie, who removed the stomach of animals, replacing it by a small bladder, and then found that the injection of drugs still led to the movements of vomiting, prove little regarding the seat of action; they only show that the peripheral irritation is not limited to the stomach alone. At the present time, antimony is rarely given as an emetic owing to the severe depression and even collapse which sometimes follow its use: in some cases absorption has occurred, with after effects bearing a resemblance to those of arsenical poisoning.

Antimony is used in small doses as an expectorant: there is no reason to believe that it has any specific action on the bronchial mucous glands or that it is excreted by the bronchioles; it acts simply as a mild irritant to the stomach, and all such irritation tends to produce a reflex increase of bronchial mucus.

The absorption of antimony is very slow, but if it is given by the mouth for some time in large doses, or injected under the skin, it produces effects very similar to those seen in chronic arsenical poisoning, such as changes in metabolism, fatty degeneration, and skin eruptions.

Antimony is also used as a diaphoretic. It is difficult to say how this action is produced. It is no doubt partly due to the dilatation of the cutaneous vessels, and to medullary reflexes from the alimentary canal.

It is excreted mainly by the fæces, but traces can be detected in the urine, bile, sweat, and milk. As in the case of arsenic, a certain degree of tolerance can be attained.

Antimony has a remarkable poisonous effect on *trypanosomes*, and as these protozoa are the cause of sleeping sickness in man and negana in animals, the future treatment of these diseases is very hopeful. If a rat be inoculated with negana it always dies in an average time of five or six days. If on the fourth day, when the blood is full of parasites, 5 milligrams of tartar emetic be injected subcutaneously, the parasites are killed and the rat usually survives and recovers completely. Arsenic and some aniline dyes produce the same type of effect, but are perhaps inferior to antimony.

Filariasis is a disease caused by a filiform worm living in the lymphatics of the trunk and extremities. The female pours out thousands of young filariæ which find their way into the blood, so that sometimes hundreds may be present in a single drop of the patient's blood. Intravenous injections of soluble antimony salts greatly reduce or cause the disappearance of the filarial embryos from the peripheral blood, presumably as a result of the destruction of the adult filaria, as the effect may last in some cases in an increasing degree for several months after cessation of the treatment.

Bilharzia is a fluke living in the portal and pelvic veins and giving rise to bladder irritation and hæmaturia in the infected patient. Tartar emetic has a direct specific effect on bilharzia in all its stages. It kills the parent worm in the portal tributaries: it penetrates the ova as they lie deposited in the tissue wall and kills the enclosed embryo.

Kala-azar is a disease common in parts of India and China, and due to a protozoon living in the spleen and bone marrow. Injections of antimony salts are reported to effect a cure.

The symptoms of poisoning by antimony generally begin with nausea, vomiting, and pain in the stomach which is not relieved by the vomiting. Death results from collapse. In the more chronic cases where antimony has been absorbed into the system, diarrhœa with typical "rice-water" stools is a usual feature; and there are cramps, as in arsenical poisoning, in which the muscles become rigid and cause severe pain. The urine is sometimes increased at first, but later it contains albumen and blood. Seven grains of tartar emetic is a dangerous dose. Treatment consists

in washing out the stomach and the administration of tannin, which forms an insoluble compound with the metal.

MATERIA MEDICA

1. **Acidum Arseniosum.**—White arsenic. As_4O_6. Soluble 1 in 10 of boiling and 1 in 100 of cold water. **Dose,** $\frac{1}{64}$ to $\frac{1}{16}$ gr. (1 to 4 mgrms.).

Preparations

1. **Liquor Arsenicalis.**—Fowler's solution. A 1 per cent. solution of arsenious acid, made by the aid of potassium carbonate. It is coloured with compound tincture of lavender.
   Dose, 2 to 8 m. (12 to 50 centimils).
2. **Liquor Arsenici Hydrochloricus.**—A 1 per cent. solution of arsenious acid in dilute hydrochloric acid. **Dose, 2 to 8 m.** (12 to 50 centimils).

2. **Sodii Arsenas Anhydrosus.**—Na_2HAsO_4. Soluble 1 in 6 in water and forming an alkaline solution. **Dose,** $\frac{1}{40}$ to $\frac{1}{10}$ gr. ($1\frac{1}{2}$ to 6 mgrms.).

Preparation

Liquor Sodii Arsenatis.—1 per cent. of anhydrous sodium arsenate in distilled water. **Dose, 2 to 8 m.** (12 to 50 centimils).

3. **Arsenii Iodidum.**—Arsenious iodide. AsI_3. Soluble in water and in alcohol. **Dose,** $\frac{1}{20}$ to $\frac{1}{5}$ gr. (3 to 12 mgrms.).

Preparation

Liquor Arsenii et Hydrargyri Iodidi. *See* Mercury.

1. **Antimonium Tartaratum.**—$(KSbO,C_4H_4O_6)_2,H_2O$. Tartar emetic. **Dose,** $\frac{1}{25}$ to $\frac{1}{8}$ gr. (2.5 to 8 mgrms.) (diaphoretic); $\frac{1}{2}$ to 1 gr. (3 to 6 ctgrms.) (emetic).

Preparation

Vinum Antimoniale.—0.4 per cent. in sherry.
Dose, 10 to 30 m.; 2 to 4 drs. as an emetic.

2. **Antimonii Oxidum.**—Antimonious oxide. Sb_4O_6. **Dose, 1 to 2 grs.** (6 to 12 ctgrms.).

Preparation

Pulvis Antimonialis.—Antimonious oxide, 1; calcium phosphate, 2. **Dose, 3 to 6 grs.** (2 to 4 dcgrms.).

3. **Antimonium Sulphuratum.**—A mixture of various sulphides and oxides, Sb_2S_5,Sb_2O_5,Sb_2S_3,Sb_4O_6, with some sulphur. **Dose, 1 to 2 grs.** (6 to 12 ctgrms.). Contained in Pilula Hydrargyri Subchloridi Composita.

CHAPTER XXVI

GENERAL ACTION OF THE HEAVY METALS

Local Action.—The heavy metals have many properties in common. They all possess a very important local action on the skin, alimentary canal, or other part to which they may be applied; and, with the exception of mercury, they are all absorbed only very slowly from the bowel, so that there is ample time for the development of the local action on the alimentary canal.

If the solution of a salt of a heavy metal capable of dissociation into ions is added to a proteid solution, an albuminate of the metal having a definite chemical combination is precipitated. This precipitate can be dissolved like the globulins by the addition of neutral salts, and it is also sometimes soluble in excess of proteid; thus, the albuminate of mercury is redissolved by albumen.

The salts of the metals are employed as astringents upon the skin and mucous membranes. They act in one of three ways:—The soluble salts of the metals may form albuminates and liberate free acid; the metal may be locally absorbed, so constricting the vessels of the part, and reducing the secretions; and, lastly, insoluble salts like those of bismuth may cover and mechanically protect the surface.

When an astringent metallic salt comes in contact with a mucous membrane it immediately forms a precipitate with the surface albumen, and, later, the superficial layer of cells is attacked and the protoplasm in part coagulated. The extent of the process depends upon the penetrating power of the metal and the nature of the precipitate. Dilute solutions of lead form a continuous sheath of insoluble albumen, which protects the underlying parts from further irritation. Nevertheless, lead should be applied only to places where absorption is not likely to occur, such as on the unbroken surface of the skin.

Besides the nature of the precipitate, the acid with which the metal is combined must receive consideration. When the metal combines with the albumen this acid is set free, and exercises any local action usual to it. A dilute solution of lead acetate produces little other effect than that of the metal, but a very strong solution may liberate sufficient acetic acid to distinctly irritate the tissues. Hydrochloric acid is much more irritant than acetic, and lead chloride is more dissociable than lead acetate; hence,

if the chloride is employed the astringent action of the lead is masked by the irritation and corrosion induced by the acid. Obviously, this irritation can be avoided by employing a suitable preparation. The albuminate of the metal is non-irritant, but it is not very efficient as an astringent, because it can no longer precipitate albumen. The double salts of the metals, likewise, do not precipitate albumen; they are decomposed only very slowly and are little liable to irritate. Combinations of the metal with organic acids, such as acetic, tartaric, or citric, also render irritant action negligible, since these salts are so slowly dissociated that only a very small percentage of acid is present at any one time. Hence, in determining the local effect of a metallic salt, both the metal and the acid require consideration.

Before leaving this local action of the salts of the metals, the fact must be noted that a certain tolerance can be acquired to the local corrosion. At present this is impossible to explain, but it has been suggested that the tolerance to arsenic may possibly come under this category.

General Action.—To produce a general action the salt must be dissociable and capable of absorption. Zinc chloride injected into an animal is very toxic because the zinc ion is free to act, but if zinc, combined with some organic radicle which renders it non-dissociable, is given under like conditions it is non-toxic. The principal differences in the actions of the metals depend upon the relative rate of their absorption. There is not a great deal of difference between the toxicity of arsenic and of iron when they are injected into the circulation of an animal, but arsenic is infinitely more toxic when given by the mouth, because it is absorbed so much more readily. Mercury is the only heavy metal which is absorbed from the alimentary canal in sufficient quantity to produce acute poisoning other than corrosive; lead, silver, tin, and iron are absorbed much more slowly, and bismuth, copper, zinc, and aluminium practically not at all. Lead, silver, and iron, having reached the circulation, are not very readily excreted, so that the metal tends to accumulate in the internal organs of the body, and ultimately gives rise to chronic poisoning.

To observe the systemic action of the metals upon animals, the salts must be injected either subcutaneously or into the circulation. For this purpose it is necessary to employ either double salts or salts combined with proteids. The symptoms develop very slowly, sometimes not till after several days: the metal, therefore, does not commence its action as soon as it has entered the circulation, but apparently only after a further slow absorption from the body-fluids into the living substance of the cells themselves. These symptoms, produced experimentally, have a general resemblance to those seen during chronic poisoning in man, and consist principally in affections of the central nervous system and disturbances of the alimentary canal. There may be hallucinations,

delusions, delirium, or stupor, indicating an action on the higher centres. Or there may be tremors, spasms, or epileptiform convulsions, pointing to an affection of the motor area; or, again, there may be paralysis due either to central lesions or, as in the case of lead, to peripheral neuritis.

The affection of the alimentary canal is shown by pain in the abdomen, flatulence, nausea and vomiting, followed by purging. The pain is sometimes of an intense colicky nature as in lead poisoning, due to the direct action of the absorbed metal on plain muscle. But, besides this, the heavy metals have a specific action like arsenic on the whole of the epithelium of the alimentary canal. The mucous membrane is swollen, and in parts may become separated from the underlying tissue. In severe cases ulceration and hæmorrhages occur. The circulatory system is comparatively little affected. Of course, in those cases where there is much effect on the alimentary canal with associated collapse, the whole circulatory system is depressed, the heart is very feeble, and the vessels are dilated. On the other hand, these metals act directly on plain muscle, and so tend to produce constriction of the vessels, and in cases of chronic poisoning, such as that by lead, the vessels may be much constricted and the blood-pressure high.

Most of the metals after absorption produce slight changes in the metabolism, which closely resemble those of phosphorus. They are all excreted by the large intestine: some are also excreted by the kidneys, and these, in large doses, may induce an acute nephritis, in which case the urine contains albumen, casts, and sometimes blood.

Colloids.—During recent times injections of colloidal solutions of various metals have been employed in therapeutics, and various speculations have been made to account for metals in a particulate form exerting a pharmacological action. Brownian movements, surface phenomena, electrical charge, catalytic action and conversion into the ionic form have all been suggested as a possible explanation. The injection of colloidal metals causes effects similar to the metal in ionic form, except that the action is slow in beginning, feeble in degree, and prolonged in time. It is probably only the very finest ultramicroscopical particles, too small to influence the polarization of light, which exert any action. The evidence points to the pharmacological action being due to the conversion of these amicrons into the ionic condition.

CHAPTER XXVII

MERCURY

THE most important physical property of the salts of mercury is their volatility. The minute state of division in which they can exist possibly accounts in part for the readiness with which they are absorbed. Mercuric chloride may be taken as a typical salt both on account of its ready solubility in water and the fact of its being easily dissociated : it precipitates egg white or serum albumen from solution, and the precipitate is soluble in excess of albumen or by the addition of a little sodium chloride. The easy solubility of the albuminate is also advanced as an explanation of the relative ease with which mercury is absorbed.

The soluble salts of mercury are even more corrosive than those of the other metals, and this is no doubt largely due to the fact that the mercury albuminate does not form a protective sheath on the mucous membrane on account of its solubility in saline solution or albumen, and so it leaves the acids free to exert their full corrosive action. The insoluble salts of mercury, such as calomel, are very much less poisonous because they do not come into contact with the living tissues very readily, and hence a soluble albuminate is formed only very slowly. On this account these salts have little or no corrosive action.

Mercury is used principally in the treatment of syphilis, and for this purpose various methods of administration are in vogue. First, there is the method of inunction, which consists in rubbing an ointment into various parts of the body in a definite order. This method has the advantage that the local action of the drug on the stomach and intestines is avoided, while it produces a moderate mercurial action extending over a prolonged period. Calomel and the various metallic preparations are given generally by the mouth ; they tend to produce diarrhœa and to derange digestion. A third method is the hypodermic : it induces the specific effects quicker and with more certainty than when the drug is given by the mouth, but it has the disadvantage of producing considerable local irritation. The irritation can to some extent be avoided by adding sodium chloride to the solution of mercuric chloride and injecting deeply, such as into the gluteal muscles. In syphilitic affections of the skin still another method is used—the mercurial vapour bath : in this, calomel or sulphide of mercury is vapourised

with steam, and so the salt is deposited in a finely divided state on the body of the patient.

External.—Mercury has a powerful and specific action on all forms of living protoplasm, and in this respect it differs from the other metals. It is used largely as an antiseptic and disinfectant: one part of the perchloride in 1,000,000 parts of water inhibits the growth of the anthrax bacillus, and a solution of 1 in 1000 is regarded as sufficient for disinfecting most fluids. For utensils, clothing, &c., 1 in 2000 is enough, and for excreta the addition of an equal bulk of 1 in 1000 is to be recommended. A solution containing 1 in 5000 or more is very useful in the treatment of infectious conjunctivitis. Mercurial ointments are used largely in skin diseases, especially in those of parasitic origin. Mercuric chloride forms a double salt with sodium chloride ($HgCl_2.2NaCl$) which, though it ionises less than $HgCl_2$, is a better germicide, since its increased solubility more than makes up for diminished dissociation. The nitrate, sulphate, and acetate of mercury are all more dissociable than the chloride and yet they are inferior antiseptics. This is due to the solubility of the chloride in lipoids, a property which is not possessed by the other salts, hence it penetrates into bacteria more easily.

Mercury has a paralysing effect on the movements of white blood-corpuscles. This is best observed in the frog by applying a little (1 in 10,000) solution of the perchloride to the highly inflamed mesentery. It will then be seen that the migration of the white blood-corpuscles through the walls of the vessels ceases, the corpuscles no longer exhibit amœboid movements, and so the suppuration is arrested. This explains how the blue ointment, when rubbed into the skin of a patient, tends to retard suppuration. Mercurial ointments are also used to reduce swellings and to promote absorption of subcutaneous effusions, and it is possible that the beneficial effect, other than that induced by the rubbing, is brought about in the manner above mentioned.

Mercurial vapour is absorbed not only by the lungs but also by the skin, for an animal placed in an atmosphere of mercury, with its head external to the apparatus, still becomes affected by the fumes, and mercury can be found in its excreta. Both the metal and its compounds, when rubbed into the skin along with fat, are absorbed and get into the circulation, the fat enabling them to pass into the hair and sebaceous follicles. How it comes to be absorbed so readily from mucous surfaces we do not know; but the volatility of mercury and its compounds, and the easy solubility of its albuminate, with a special affinity for lecithalbumen, are certainly important factors in the process.

If the more insoluble preparations of mercury, such as calomel, are injected subcutaneously, they can be detected in the white blood-corpuscles, and it is quite likely that these corpuscles play an important *rôle*, as in the case of arsenic and iron, in the absorption of this drug from the alimentary canal.

Alimentary Canal.—Mercury produces a very decided effect upon the mouth; it is not reflex, for it occurs only after absorption of the metal into the system. First, a metallic taste is experienced, then the breath becomes unpleasant, and the secretion of saliva, which contains the metal, is much increased. Therapeutically, of course, mercurial treatment is stopped when this salivation is noticed, but if large doses of the metal have been given, ulceration is likely to occur round carious teeth, and if this extends to the bone periostitis and ultimately necrosis are induced. Mercury, then, has a special action on the salivary glands after its absorption into the substance of the cells, and this effect is produced no matter in what form or by what way it is administered.

Calomel and blue pill are the forms in which mercury is usually given to obtain the effect upon the stomach and intestine; this is on account of their insolubility and the fact that comparatively little of the metal is absorbed into the system. They act as very mild purges by slightly irritating the intestines, and are mostly excreted unchanged in the fæces. They also tend to prevent the growth of bacteria, and so limit putrefaction within the bowel.

Mercury is often regarded as a cholagogue, but it does not increase the flow of bile from the liver. Nevertheless, it does cause the appearance of bile in the fæces, for the green tint of the stools after purgation by calomel is due to bile. This has been ascribed to the antiseptic properties of mercury checking the growth of bacteria in the gut, and so preventing the normal conversion of bile pigments into stercobilin, the normal colouring matter of the fæces.

Even when calomel and metallic mercury are used, a small proportion of the mercury is absorbed into the system, produces typical specific effects, and is excreted again into the cæcum and colon: if more soluble preparations of the drug are used or if it is injected, an acute inflammation of the lower gut results. In such cases the mucous membrane of the cæcum and colon becomes swollen, red, and injected, ulceration occurs, and the condition leads to a train of symptoms such as are seen in cholera or acute arsenical poisoning, viz. pain, tenesmus, and rice-water stools, the fæces containing blood and fragments of mucous membrane.

Mercury is employed in therapeutics as a mild purgative, and as a general disinfectant to the alimentary canal: it is used also in certain forms of diarrhœa, in dysentery, cholera, and enteric fever, generally with the object of disinfecting the stools.

The medicinal use of mercury seldom leads to very definite effects on the central nervous system. Tremor is the most constant symptom of chronic mercurialism: it generally begins in the lips and tongue, and later affects the upper extremities. It is particularly marked during voluntary movements. Sometimes there is paralysis resembling that of lead, with "dropped wrist," wasting of the muscles affected; and sometimes persistent facial neuralgia and

other pains in the head and limbs: hallucinations and delusions are also occasionally present. These effects are cerebral, but therapeutically they are of little importance. Formerly it was thought by a few that some of the symptoms of tertiary syphilis might be due to mercury; this has been shown to be false.

Mercury has a specific action in syphilis, especially in secondary and congenital syphilis. In tertiary syphilis its action is inferior to the iodides. It acts by destroying the specific spirochæta of Shaudinn. Metchnikoff has shown that if the syphilitic virus is injected into men or monkeys, the development of the disease is completely prevented if a mercurial ointment is rubbed into the seat of inoculation an hour or two afterwards. Mercury is also specific in secondary syphilis, when the organism, instead of being localised as in primary sores, has obtained access to the circulation. But to effect a cure it is generally regarded as necessary to continue mercurials for several months, and even then relapses are not very uncommon, long after every symptom has been relieved. The drug is certainly carried by the blood to the syphilitic lesion, and is said to be stored up as albuminate.

The evidence with regard to the action of mercury on nutrition is very contradictory, principally for two reasons: (1) the dosage of the metal in the different experiments which have been undertaken has been very varied; and (2) the effect upon the digestive organs has not received sufficient consideration. It has been found that the administration of small doses of mercury to rabbits, dogs, and men causes an increase in the number of red blood-corpuscles, while the body gains weight. Larger doses act in the reverse way; both the hæmoglobin and corpuscles are diminished, and the animal loses weight. It has not been shown how these effects come about.

Small doses of mercury diminish the amount of oxidation of the tissues, as shown by variations in the gaseous interchange, and there is a slight increase in the nitrogenous output in the urine. They diminish the alkalinity of the blood by an excessive production of lactic acid, and also slightly increase the rate of growth of the bones in young animals. In all these respects the action of mercury resembles that of phosphorus and arsenic.

The circulatory and respiratory systems are only indirectly affected during poisoning.

Mercury is excreted mainly by the cæcum and colon, and is discharged in the fæces as the sulphide. Some is excreted in the urine and saliva. After the administration of the perchloride by the mouth the metal can be detected in the urine in two hours, and in the saliva in about four hours. During its excretion by the kidneys it causes slight irritation, and somewhat increases the flow of urine. The exact cause of this diuresis, which is seen best after taking calomel, is unknown, but it is stated not to be due to irritation of the renal epithelium. Large doses of mercury produce acute nephritis and necrosis of the epithelium of the tubules: the necrosed

tubules are often filled with a deposit of calcium phosphate. This action on the kidneys is important, for albumen and casts are not infrequently found in the urine of syphilitic patients undergoing mercurial treatment, and necessitates the treatment being stopped for a time. The elimination of mercury, like that of the other metals, is slow. It quickly passes out of the blood and becomes fixed in the tissues. It is then found in largest amount in the liver, spleen, and kidneys: some is also found in the mucous membrane of the cæcum and colon, no doubt in process of excretion. The more rapidly mercury appears in the urine the more intense is its action, and the curve of urinary elimination serves to determine the value of the different methods of administering mercury, the quantity in the urine varying with that in the blood.

Mercurial poisoning may be acute or chronic. Supposing a drachm of corrosive sublimate has been swallowed, there is immediate burning in the mouth followed by intense gastric pain. Vomiting, colicky pains, and great abdominal tenderness follow; later this is succeeded by tenesmus, purging, and sometimes suppression of urine. Death ensues in the course of a few hours from collapse.

The best antidote is albumen, such as egg-white, wheat-flour, and milk: emetics must follow, otherwise the mercury may be absorbed. Common salt should not be used as an emetic, as this would increase the solubility of the albuminate.

The repeated ingestion of small doses of mercury leads to pronounced salivation, fœtid breath, swollen and ulcerated gums, and may induce periostitis of the bone; there may be also nausea, colicky pains, and some diarrhœa. Perhaps the most characteristic effect of chronic poisoning is the mercurial paralysis. It especially affects those who are exposed to the fumes of the drug, such as the makers of barometers and thermometers and water-gilders. The tongue, lips, and upper limbs are affected first, but later the whole muscular system may be involved. All voluntary movement is associated with tremors, which are observed only when the muscles are acting, and cease during sleep. Delirium and mania are observed occasionally. Chronic mercurial poisoning also affects metabolism, and gives rise to cachexia and fatty degeneration of the various organs as in the case of phosphorus.

MATERIA MEDICA

1. Hydrargyrum.

Preparations containing Free Mercury

1. **Hydrargyrum cum Cretâ.**—Grey powder. 1 of mercury with 2 of chalk. The mercury is liable to become mercuric oxide with age. **Dose, 1 to 5 grs.** (6 to 30 ctgrms.).
2. **Emplastrum Hydrargyri.**—1 in 3 of mercury.
3. **Linimentum Hydrargyri.**—Containing ammonia and camphor. Mercury 1 in 10.

4. Pilula Hydrargyri.—Blue pill. Mercury 1 in 3.
Dose, 4 to 8 grs. (25 to 50 ctgrms.).
5. Unguentum Hydrargyri.—Blue ointment. Mercury 30 per cent.
6. Unguentum Hydrargyri Compositum.—Scott's ointment. Contains camphor. 12 per cent. of mercury.

2. Hydrargyri Perchloridum.—Corrosive sublimate, $HgCl_2$. Dose, $\frac{1}{32}$ to $\frac{1}{16}$ gr. (2 to 4 mgrms.).

Preparations

1. Liquor Hydrargyri Perchloridi.—0.1 per cent.
Dose, 30 to 60 m. (2 to 4 mils).
2. Lotio Hydrargyri Flava.—Yellow wash. The yellow oxide is formed by means of lime water thus :—$HgCl_2 + CaH_2O_2 = HgO + CaCl_2 + H_2O$. 2 grs. in the oz.

3. Hydrargyri Subchloridum.—Calomel. Dose, $\frac{1}{2}$ to 5 grs. (3 to 30 ctgrms.).

Preparations

1. Pilula Hydrargyri Subchloridi Composita.—Plummer's pill. Calomel, sulphuretted antimony, guaiacum resin.
Dose, 4 to 8 grs. (25 to 50 ctgrms.).
2. Lotio Hydrargyri Nigra.—Black wash. Mercurous oxide is formed by the addition of lime water thus :—$Hg_2Cl_2 + CaH_2O_2 = Hg_2O + CaCl_2 + H_2O$, 3 grs. to 1 oz.
3. Unguentum Hydrargyri Subchloridi.—20 per cent.

4. Hydrargyri Oxidum Rubrum.—HgO.

Preparation

Unguentum Hydrargyri Oxidi Rubri.—10 per cent. Red precipitate ointment.

5. Hydrargyri Oxidum Flavum.—HgO.

Preparation

Unguentum Hydrargyri Oxidi Flavi.—2 per cent.

6. Hydrargyrum Oleatum.—Does not ionise.

Preparation

Unguentum Hydrargyri Oleati.—1 in 4.

7. Hydrargyri Iodidum Rubrum.—HgI_2. Dose, $\frac{1}{32}$ to $\frac{1}{16}$ gr. (2 to 4 mgrms.).

Preparations

1. Liquor Arsenii et Hydrargyri Iodidi.—Donovan's solution. Equal parts of arsenious and mercuric iodides in water, 1 per cent. of each iodide. Dose, 5 to 20 m. (3 to 12 decimils).
2. Unguentum Hydrargyri Iodidi Rubri.—4 per cent.

8. Liquor Hydrargyri Nitratis Acidus.—Contains 60 per cent. $Hg(NO_3)_2$, with about 11 per cent. HNO_3.
9. Unguentum Hydrargyri Nitratis.—Citrine ointment.

PREPARATION

Unguentum Hydrargyri Nitratis Dilutum.—1 in 5.

10. **Hydrargyrum Ammoniatum.**—White precipitate, NH_2HgCl. Prepared from ammonia and corrosive sublimate :—

$$HgCl_2 + 2NH_4OH = NH_2HgCl + NH_4Cl + 2H_2O.$$

PREPARATION

Unguentum Hydrargyri Ammoniati.—White precipitate ointment. 5 per cent.

Sal Alembroth.—A double chloride of mercury and ammonium, a powerful antiseptic and less irritating than perchloride of mercury. (Not official.)

CHAPTER XXVIII

IRON

Iron is essential for life in the higher plants and animals. Its presence is especially important on account of its relation to pigment formation. Chlorophyll, the green colouring matter of plants, is not formed in the absence of iron ; and the metal enters into the composition of the hæmoglobin of animals. In the body hæmoglobin is always being broken down and excreted as colouring matter in the urine and fæces, and, therefore, iron must be absorbed into the system to replace the loss : under ordinary conditions this is provided in the vegetable and animal substances of the food.

The local action of iron salts is like that of other metals. The insoluble preparations have no effect on the skin or alimentary canal except in so far as they are converted into soluble compounds by the excretions. Thus, ferrous carbonate is partially converted into ferrous chloride in the stomach, and so the properties of this latter soluble salt are developed.

Ferrous salts combine with albumen and gelatin, forming soluble compounds which are neither irritating nor corrosive. Ferric salts, however, precipitate albumen, with which they form an insoluble compound ; they are in consequence irritant and astringent. For this reason ferric chloride is used as a styptic, that is, a drug which stops bleeding; for example, after post-partum hæmorrhage the cavity of the uterus is sometimes swabbed with a strong solution of ferric chloride, where it acts by coagulating the proteids of the blood. This is not without danger, as clots have been known to escape into the circulation and cause embolism. The soluble and dissociable salts of iron are antiseptic and disinfectant, principally by reason of their action on albumen.

If salts of iron are taken by the mouth as a medicine they have a characteristic chalybeate taste, and blacken the gums and teeth. On reaching the stomach they exercise an astringent action, and if used over a prolonged period cause dyspepsia. In the intestines the astringent action of iron is continued and results in constipation; the fæces become hard, dry, and black, the last from the formation of iron sulphide.

Large doses of the more corrosive iron salts induce vomiting, abdominal pain, and sometimes diarrhœa, followed by collapse and death.

If the metal in the form of the double salt of iron and soda is injected into animals it produces violent vomiting, diarrhœa, and again, death from collapse. There is also a gradually increasing paralysis of the central nervous system, sometimes associated with a few convulsive movements. The urine contains blood, albumen, and casts, and post-mortem the kidney is found inflamed. These effects are only of scientific interest, for when the drug is given by the mouth symptoms of this kind are never developed. Nevertheless, a very small percentage of the iron taken by the mouth is absorbed and, after passing into the system, excreted by the large intestine. It is probable that the other heavy metals are absorbed and excreted in a similar manner; but as the movements of this metal in the body have been worked out more fully, they will serve as a type for all. When the amount of iron present in the alimentary canal is small, absorption goes on from a limited portion of the small intestine, beginning an inch or two from the pylorus and, in the case of man, extending only some twelve to twenty inches downwards. In whatever form the iron reaches the stomach, probably a portion of it is converted by the hydrochloric acid into ferrous chloride, in which form it combines with albumen, and on reaching the duodenum is decomposed by the alkali into the carbonate: many of the organic salts of iron do not undergo this change into the insoluble carbonate. But whether the iron is present in a soluble or in an insoluble form, absorption of iron granules takes place through the epithelial cells. These granules are taken up by the leucocytes of the mucosa, and ultimately are carried into the portal vein, although some find their way into the mesenteric glands. Iron, like most of the metals, is excreted more slowly than it is absorbed. The excess is stored up in the liver, and to some extent in the spleen and bone-marrow. In the liver the iron enters into more or less complex combination with albumens, and one such body, ferratin, has been isolated by Schmiedeberg. It contains a proportion of iron varying from 4 to 8 per cent. The liver should be regarded not only as a storehouse for iron but a place in which it can be worked up into more or less complex ferruginous organic compounds, to be again doled out to the bone-marrow as required for the manufacture of the red blood-corpuscles.

The liver thus prepares the iron for hæmoglobin formation, and the organ appears to be indifferent as to the form in which the iron reaches it.

Excretion takes place by the rectum; but a minute amount is also discharged in the urine. That iron is absorbed and excreted in the manner described the following experiments show:—

(1) *Microscopical.*—If a meal containing some iron is given to an animal, and if after a suitable interval it is killed and various parts of the alimentary canal are hardened in alcohol, microscopical sections of these show distinct evidence of iron in process of absorp-

tion and excretion. The stains most suitable for demonstrating the iron are: (*a*) potassium ferrocyanide and hydrochloric acid, which colour the granules blue but have no effect on hæmoglobin; and (*b*) ammonium sulphide, which stains the granules black.

Fig. 86 shows a section across the duodenum stained with ammonium sulphide, in which the absorption of iron can be followed

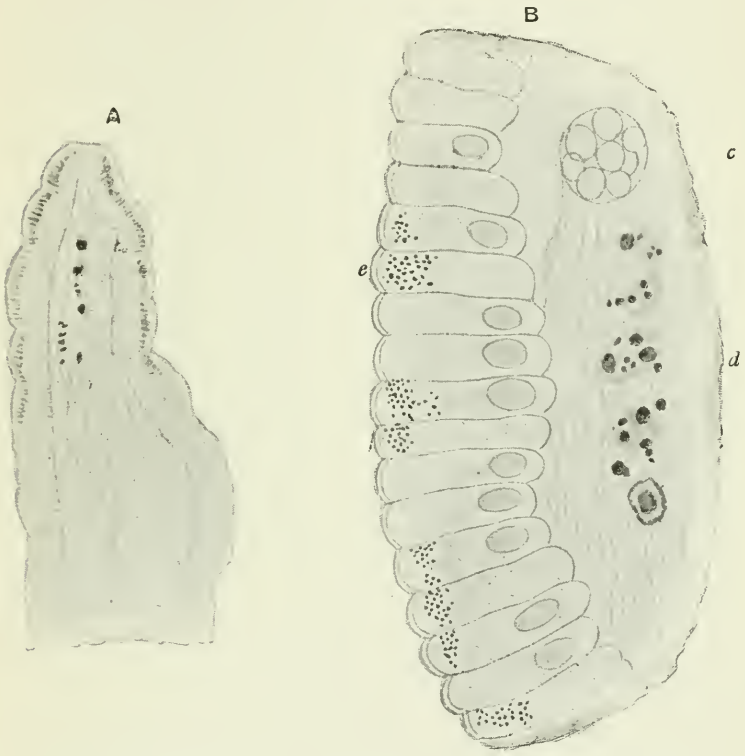


FIG. 86.—ABSORPTION OF IRON FROM THE INTESTINAL MUCOSA.

A = section of a villus of a guinea-pig (low power) stained with ammonium sulphide. The position of the iron during absorption is shown by the dark portions. B = a portion of the same under a high power. Note the presence of iron in the epithelial cells, at *e*; from these it is transferred either to the blood-plasma or to the sub-epithelial leucocytes and so to the general circulation. Granules of iron sulphide in the leucocytes are shown in the figure at *d*. *c* represents a small capillary. (The intestine was laid open immediately after removal, was quickly washed free from adherent food and dropped into alcohol.)

through the mucous membrane to the leucocytes in the manner already described. Such preparations, of course, can be obtained only from the limited portion of the duodenum and rectum where absorption and excretion respectively occur.

(2) *Chemical.*—If an animal which has had a meal containing iron is killed, and if its alimentary canal is slit up, pinned out on a suitable surface, and painted with ammonium sulphide solution,

two zones are conspicuously stained black, one in the duodenum and the other in the rectum. If the mucous membrane is washed, separated from the muscular tissue, and cut transversely into a number of pieces, the organic matter can be burnt off, and the exact amount of iron in each segment determined. It is much greater in the duodenum than in the rest of the small intestine, and it is found again in considerable amount in the rectum.

Another method of demonstrating absorption is to feed two sets of mice on cheese, that supplied to one set containing iron. After a week all the mice are killed, skinned, and deprived of their alimentary canals; and the amount of iron in their tissues is estimated. The analyses show that those fed on cheese containing iron always yield a far larger percentage of the metal than the other set, sometimes nearly twice as much; nevertheless, there is a limit to the absorption of iron compounds by the body, to overstep which means death. Again, if goats are supplied with iron in their food their milk contains an increased percentage of the metal. But perhaps the most conclusive proof is the following:—An animal upon which colotomy had been performed was treated with iron by the mouth. The lower portion of the gut was washed out daily and the washings analysed. Although the upper bowel discharged by way of the colotomy wound, yet a small amount of the drug was found in this lower gut, where it could only have arrived by a process of excretion.

There is, then, very definite evidence that iron is absorbed, stored up in the body, and ultimately excreted into the rectum.

Iron is used principally in the treatment of anæmia. If the anæmia is that due to simple loss of blood, unaided recovery gradually takes place, but if iron is given the blood improves much more rapidly. In the anæmia, which may follow any form of disease, iron also improves the blood and so favours the recovery of the patient. The principal use of this drug is in chlorosis. This is an anæmia especially common in young girls, and probably due to the non-absorption of iron by the alimentary canal. In these cases there is a great deficiency of hæmoglobin in the blood, but the number of red corpuscles is relatively unaltered, so that each corpuscle becomes paler. In chlorosis also the tissues contain abnormally large amounts of water. Bunge believes that the iron which is absorbed normally is obtained from the organic iron of the food, and in chlorosis he considers that digestion is disturbed by the formation of sulphides, and that these form sulphide of iron, which cannot be absorbed. When inorganic iron is administered it neutralises the sulphides, and thus protects the organic iron in the food, which is then absorbed. Before discussing this hypothesis, it must be remembered that the anæmia is due solely to a deficiency of iron, and is brought about by inefficient absorption from the alimentary canal. Consequently, iron preparations administered subcutaneously should cure chlorosis, and this is found to be the

case no matter in what form the iron is injected. Bismuth and manganese take up sulphides quite as well as iron, but they do not cure anæmia. On the whole, Bunge's speculation that sulphides in the bowel bring about chlorosis finds little support from the evidence at present available. There is no doubt that some unknown factor is at work limiting the normal absorption of iron. One other important action of iron has been determined from the histological examination of the bone-marrow. Iron exerts a stimulating action on this tissue ; this has been shown by the fact that if the bone-marrow of young animals is rendered anæmic artificially, the administration of iron with the diet causes an increase in the nucleated red cells far in excess of that observed in control animals.

The increase in the blood-plasma which has been put forward as a cause of chlorosis is probably only a secondary effect.

In chlorosis, then, iron exerts a double action : the absorption of iron and its utilisation in the synthesis of hæmoglobin are facilitated, and further, protein substances rich in iron are stored up in the liver and spleen; secondly, iron stimulates in a specific manner those cells which form hæmoglobin.

In " pernicious anæmia " there is increased breakdown of red blood-corpuscles and a relatively insignificant deficiency of hæmoglobin in the corpuscle ; here the sound corpuscles are destroyed. This condition rarely improves after iron.

Iron should be given after meals to minimise its local action upon the alimentary canal. All preparations of iron cure chlorosis, and the choice of a preparation must be guided by the condition of the gastro-intestinal tract (*see* p. 403).

MATERIA MEDICA

1. **Ferrum.**—Iron wire free from oxide.

PREPARATION

Vinum Ferri.—Made with sherry. 1 in 20.
Dose, 1 to 4 drs. (4 to 16 mils).

2. **Ferrum Redactum.**—Reduced iron. Contains about 25 per cent. of oxide. Dose, 1 to 5 grs. (6 to 30 ctgrms.).

PREPARATION

Trochiscus Ferri Redacti.—1 gr. in each.

3. **Ferri Sulphas.**—$FeSO_4.7H_2O$. Dose, 1 to 5 grs. (3 to 30 ctgrms.).

PREPARATION

Mistura Ferri Composita.—" Griffith's mixture." Ferrous sulphate, potassium carbonate, myrrh. It contains iron carbonate, for the iron sulphate and the potassium carbonate react together.
Dose, ½ to 1 oz. (15 to 30 mils).

4. Ferri Sulphas Exsiccatus.—$2FeSO_4.3H_2O$. Dried sulphate of iron. Dose, ½ to 3 grs. (3 to 20 ctgrms.) in pill.

PREPARATIONS

1. Pilula Ferri.—Blaud's pill. Contains exsiccated ferrous sulphate and exsiccated sodium carbonate. Each contains 1 gr. ferrous carbonate; the same change takes place as in Mistura Ferri Composita.
   Dose, 5 to 15 grs. (3 to 10 dcgrms.).
2. Pilula Aloes et Ferri.
   Dose, 4 to 8 grs. (25 to 50 ctgrms.).

5. Liquor Ferri Perchloridi Fortis.—Contains about 20 per cent. of iron.

PREPARATIONS

1. Liquor Ferri Perchloridi.—1 in 4.
   Dose, 5 to 15 m. (3 to 10 decimils).
2. Tinctura Ferri Perchloridi.—1 in 4.
   Dose, 5 to 15 m. (3 to 10 decimils).

6. Liquor Ferri Persulphatis.—$Fe_2(SO_4)_3$.
7. Ferri et Potassii Tartras.—Soluble 1 in 4 in water. Dose, 5 to 10 grs. (3 to 6 dcgrms.).
8. Ferri et Ammonii Citras.—Very soluble in water. Contains 16 per cent. iron. Dose, 5 to 10 grs. (3 to 6 dcgrms.).

PREPARATION

Vinum Ferri Citratis.—Made with orange wine.
Dose, 1 to 4 drs. (4 to 16 mils).

9. Ferri et Quininæ Citras.—Very soluble in water. Dose, 5 to 10 grs. (3 to 6 dcgrms.).
10. Ferri Phosphas Saccharatus.—Consists of ferrous phosphate, ferric phosphate, and iron oxide. Dose, 5 to 10 grs. (3 to 6 dcgrms.).

PREPARATIONS

1. Syrupus Ferri Phosphatis.—1 gr. of ferrous phosphate in each drachm.
   Dose, ½ to 1 dr. (2 to 4 mils).
2. Syrupus Ferri Phosphatis cum Quinina et Strychnina.—Easton's syrup. Each dr. represents 1 gr. of ferrous phosphate, ⅘ gr. of quinine sulphate, and $\frac{1}{32}$ gr. of strychnine.
   Dose, ½ to 1 dr. (2 to 4 mils).

11. Ferri Carbonas Saccharatus.—Ferrous oxycarbonate, $xFeCO_3yFe(OH)_2$, mixed with sugar. The carbonate, $FeCO_3$, forms about one-half of the mixture; it is an unstable body and is slowly transformed to ferric hydrate, $Fe_2(OH)_6$. Dose, 10 to 30 grs. (6 to 20 dcgrms.).
12. Syrupus Ferri Iodidi.—Contains 5 per cent. by weight of ferrous iodide. Dose, 30 to 60 m. (2 to 4 mils).

Unofficial Drugs.—Of the protein compounds of iron the following are some of the more important :—

Ferratin.—The form in which iron exists in this substance is said to be identical with that in which it exists in the liver. It is partially decomposed in the stomach into inorganic salts. It contains about 7 per cent. of iron. **Dose, 8 to 20 grs.**

Hæmatogen and **Carniferrin** are organic compounds of the same type as Ferratin.

Hæmoglobin has been lately employed. It is converted to hæmatin in the stomach, and for the most part, if not entirely, it passes through the bowels without being absorbed.

Hæmol and **Hæmogallol** are prepared by the action of reducing agents on blood.

In the treatment of chlorosis the organic compounds are all distinctly inferior to the inorganic preparations. They have the advantage of being non-irritant to the stomach, but in the future they will probably be used less and less.

CHAPTER XXIX

METALS USED FOR THEIR ASTRINGENT PROPERTIES

Lead, Bismuth, Cerium, Silver, Aluminium, Copper, Zinc, Chromium, Manganese

LEAD

Lead is used in medicine as an astringent application during inflammation of the skin. It is also employed in various forms of diarrhœa, and occasionally with the object of stopping internal hæmorrhage.

Solutions of lead precipitate albumen: the albuminate is dense and heavy, and is not soluble in excess of albumen nor in neutral salt solutions. Therefore, when such a precipitate is formed upon a mucous membrane, it affords a protection against the further penetration of the metal. The salt of lead most generally employed for this purpose is the acetate, in which the irritation of the acetic acid is so slight that it may be neglected, and the effect of applying such a solution may be regarded as that of the astringent action of the metallic ion alone.

When lead is taken by the mouth lead albuminate is formed, only a trace of which is taken into the system. The absorption goes on very slowly, and the effect of a sudden absorption of lead in man, such as may occur with mercury, is unknown. Nevertheless, it reaches the blood more rapidly than the other heavy metals except mercury, and is very gradually stored up in the tissues; as it is excreted even slower than it is absorbed, cumulation occurs. In these days when lead is so extensively used for all kinds of industrial purposes, and when we receive our drinking water through lead pipes, plumbism is so common that it is convenient to consider the pharmacology of the metal from the cases of chronic poisoning.

The first sign of poisoning may be *anæmia*, with a disagreeable metallic taste in the mouth when waking in the morning. Sometimes *colic* is the first symptom of which the patient complains: it begins with a severe pain in the abdomen near the umbilicus and is accompanied by obstinate constipation and often by vomiting. This colic is probably muscular in origin. Lead, like barium, has a specific action on *muscle-fibre;* it increases the tonus and excites

automatic contractions in all plain muscular tissue throughout the body. Drugs which excite any part of the motor nervous mechanism of the intestines increase the peristalsis, that is, produce a co-ordinated series of muscular contractions resulting in the more rapid passage downwards of the intestinal contents. But drugs like barium or lead do not act so: they excite the muscle directly, and produce localised rings of contraction in parts of the gut; these gradually relax, and the contraction rings pass to another portion of the gut, but there is no ordered sequence and no pronounced increase of peristalsis. This effect is easy to observe, and can still be obtained in a piece of isolated intestine from which Auerbach's plexus has been removed.

The effect on the *uterus* is another example of the action of lead on plain muscle. Women exposed to the fumes of lead suffer from menorrhagia, and if pregnant they commonly miscarry. The ecbolic action of lead salts is beyond all dispute. The action on plain muscle is also seen in the *vascular system:* the peripheral vessels become constricted and the blood-pressure rises. This contraction of the vessels was formerly thought to be reflex caused by the pain; it is well recognised that any severe and sudden pain or emotion will send up the blood-pressure, but this is not the cause here, for in chronic lead poisoning the contraction of the vessels is permanent, while the pains are spasmodic. Lead affects the heart-muscle in much the same way: it increases the tonus of the heart, but not its power of doing work; on the contrary, the actual efficiency of the heart is diminished.

One characteristic sign of the presence of lead in the system is the *blue line* which occurs at the margin of the gums and teeth. It is due to a deposit of lead sulphide in the tissues around the vessels as the lead passes out from the blood, the sulphur being provided by the tartar of the teeth. In some instances the tongue also may become blue. Bismuth and silver salts, if taken over a prolonged period, have been known to produce a somewhat similar bluish-black line on the gums.

In some people lead seems especially to pick out the *nervous system* for attack. A common feature of chronic poisoning is paralysis of the extensors of the wrists and fingers, leading to "wrist-drop." In this extensor paralysis the supinator longus is unaffected. The paralysed muscles quickly atrophy and give the reaction of degeneration. The effect, in probably every case, begins as a neuritis, like that of arsenic. Microscopical sections of such nerves show an increase in their connective tissue. Changes are sometimes found in the anterior horns of the grey matter of the cord, in the cells of the posterior roots and in the brain, but these are probably secondary to the interstitial neuritis.

Lead has a direct action on *striped muscle*, which becomes very easily exhausted, and loses its power of responding to stimulation. It is similar to that shown in Fig. 39, which represents the contractions

of a frog's gastrocnemius as the result of single induction shocks, taken some hours after an injection of cocaine. In chronic lead poisoning the muscle-fibres are sometimes degenerated, and the nuclei in the interstitial tissue increased in number.

Now in man the nervous and muscular symptoms of lead poisoning are only evident after poisoning lasting weeks or months. If animals are poisoned with an organic lead compound like the triethylate of lead, penetration into nerve and muscle is very rapid, owing probably to its physical properties, and symptoms of chronic lead poisoning can be produced in two or three days. The same fact holds good for the mercury and arsenic compounds, which as a result of their peculiar distribution act in situations which ordinarily they do not reach.

Workers in lead may be affected with epileptiform convulsions, in which they die, or recover often to find themselves blind. An examination of the retina in these cases reveals optic neuritis, retinitis, and sometimes hæmorrhages. This effect is not always the result of uræmia, as it occurs when there is neither albumen in the urine nor other signs of nephritis. Affections of the cerebrum occasionally occur, and are shown by general muscular weakness, staggering gait, trembling lips and tongue, embarrassment of speech, and loss of memory. Somewhat similar symptoms can be obtained in animals by the injection of lead; thus, dogs show tremors, chorea, and epileptiform convulsions. In most cases these convulsions are due to the special action of the lead on the cerebral cells, which post-mortem are found degenerated; but they are not always so caused, for, on chemical analysis of the brain after death during convulsions, it is common to find no trace of the metal in the cerebrum. In these cases the convulsions are uræmic.

Excretion is gradual, and takes place mainly by the fæces in the form of lead sulphide, and slightly by the kidneys in some organic combination; the urine generally contains only a trace of lead, less than one milligram a day. The gradual action of the lead on the kidneys leads to inflammation of the interstitial tissue, and ultimately to contracted granular kidney. At first there is generally some inflammation of the tubules, and later in the disease the interstitial proliferation is most marked. The ordinary symptoms of contracted granular kidney follow.

Lead diminishes the excretion of uric acid, and is regarded as a predisposing cause of gout.

The treatment of chronic lead poisoning should be preventive as well as curative. If lead salts have been taken by the mouth, the administration of drinks containing sulphuric acid will form the insoluble sulphate of lead. Milk or albumen may also be given to form the lead albuminate.

When the lead is in the system potassium iodide aids in its excretion. Olive oil and morphine may be used to relieve the colic.

MATERIA MEDICA

1. **Plumbi Acetas.**—$Pb(C_2H_3O_2)_2,3H_2O$. Sugar of lead. Soluble to 40 per cent. in water. **Dose, 1 to 5 grs. (6 to 30 ctgrms.).**

PREPARATIONS

1. **Pilula Plumbi cum Opio.**—Lead acetate, 6; opium, 1. 1 of opium in 8.
   Dose, 2 to 4 grs. (12 to 25 ctgrms.).
2. **Suppositoria Plumbi Composita.**—1 gr. of opium and 3 grs. lead acetate in each.
3. **Unguentum Plumbi Subacetatis.**
4. **Liquor Plumbi Subacetatis Fortis.**—24 per cent. of the subacetate, $Pb_2O(C_2H_3O_2)_2$.
5. **Liquor Plumbi Subacetatis Dilutus.**
6. **Glycerinum Plumbi Subacetatis.**—Strong solution of lead acetate.

2. **Plumbi Oxidum.**—PbO. Litharge.

PREPARATION

Emplastrum Plumbi.—Lead oleate, sometimes called lead soap. Lead oxide is boiled in water and olive oil. $3PbO + 3H_2O + 2(C_3H_5,3C_{18}H_{33}O_2) = 3(Pb2C_{18}H_{33}O_2)$, lead oleate, $+ 2(C_3H_5, 3OH)$, glycerin. Lead oleate does not ionise.

Emplastrum Plumbi is contained in Emplastra Hydrargyri, Plumbi Iodidi, Resinæ, and Saponis.

3. **Plumbi Iodidum.**—Lead iodide. PbI_2.

PREPARATION

Unguentum Plumbi Iodidi.—Made with benzoated lard.

BISMUTH

Bismuth salts are not prescribed for their effect after absorption, but entirely for their local action. The subnitrate and other preparations are sometimes employed externally as dusting powders; the former is considered to be astringent and antiseptic. Both actions depend upon free nitric acid which is liberated in the presence of water. It is also used as a snuff in irritable conditions of the nasal mucous membrane. The bismuth salt *per se* acts purely as a protective. Cases of poisoning have arisen from the subnitrate characterised by cyanosis and methæmoglobnuria and due to the formation of nitrites.

When given by the mouth, the preparations of bismuth act physically; they form an adhesive coating on the wall of the stomach and so protect it from the irritation of the food and secretions; some of them, such as the subnitrate, are also mild astringents and antiseptics. Being heavy, these salts also aid the stomach in removing the mucoid slime, which in diseased conditions clings

to the mucous membrane. Lower down in the small intestine they still act as a protective covering to the mucous membrane, and thus diminish the stimulation of the bowel by the food and secretions contained therein, and consequently lessen peristalsis. Bismuth salts, therefore, act in this situation much as a lead lotion acts when applied to an inflamed part of the skin; they are largely used in all forms of gastric affection and in diarrhœa. The fæces become black by the formation of the sulphide (Bi_2S_3).

The fœtid odour of the breath observed after taking bismuth preparations is caused by tellurium, which is apt to be present as an impurity. A minute amount of bismuth is absorbed by the mucous membrane of the small intestine, but it is extremely doubtful if symptoms of poisoning can arise from such administration under ordinary conditions. Formerly the preparations of bismuth were contaminated with arsenic and other metals, so that many of the so-called cases of bismuth poisoning were really due to the contaminating metal. Since, however, the drug has been used as a dusting powder true cases of poisoning have occurred. They generally begin with ulcerations in the mouth and other signs of acute stomatitis, which may be so severe as to lead to local gangrene. Vomiting and diarrhœa follow and the urine generally contains albumen. Death, which, however, is very rare, results from collapse. Post-mortem there is gastro-enteritis with occasional ulceration; the cæcum appears quite black, and the coloration extends through the whole of the bowel wall. This is due to the excretion of the bismuth. It has been suggested that the ulceration, which is especially prone to occur near the cæcum, might arise from the precipitation of bismuth sulphide in the vessels, so inducing a local gangrene. The kidneys also show signs of inflammation. If a double salt of bismuth, such as the ammonio-citrate, is injected into a mammal somewhat similar symptoms are produced: these are stomatitis and gastro-enteritis, followed by periodic convulsions.

Bismuth is excreted mainly by the cæcum and neighbourhood, and to a smaller extent by the kidney. Bismuth, when absorbed, is stored up in the liver like the other heavy metals. There is no reason to suppose that any of the salts of bismuth differ materially in their action. The soluble preparation, liquor bismuthi et ammonii citratis, is decomposed in the stomach, and the oxychloride is deposited as a white precipitate. Bismuth subgallate (dermatol) has been advocated as a dusting powder on ulcers and burns; it is less liable to be absorbed than some of the other salts, but has no other advantages. Neither the salicylate nor subgallate is astringent like the subnitrate; one objection to the latter salt is the fact that certain fermentations in the large intestine liberate nitrites.

MATERIA MEDICA

1. **Bismuthi Subnitras.**—$BiONO_3,H_2O$. Insoluble in water. **Dose, 5 to 20 grs.** (3 to 12 dcgrms.).

PREPARATION

Liquor Bismuthi et Ammonii Citratis.—Contains the equivalent of 5 per cent. bismuth oxide. **Dose, ½ to 1 dr.** (2 to 4 mils).

2. **Bismuthi Carbonas.**—$2(Bi_2O_2CO_3),H_2O$. **Dose, 5 to 20 grs.** (3 to 12 dcgrms.).

PREPARATION

Trochiscus Bismuthi Compositus.—Each contains 2 grs. bismuth oxycarbonate.

. **Bismuthi Salicylas.**—Insoluble in water. **Dose, 5 to 20 grs.** (3 to 12 dcgrms.).

SILVER

Nitrate of silver, like the salts of the other heavy metals, coagulates albumen, and the precipitate so formed turns black under the influence of light. When this salt is applied in the pure state to living tissues it forms a thick coating of white albuminate. The caustic action is not deep because the albuminate prevents further penetration by the salt. Lunar caustic is employed to destroy small growths on the skin.

Dilute solutions of silver nitrate are actively disinfectant both on account of the precipitation of albumen and possibly of a further specific action. Such solutions are also employed as astringents in chronic inflammation: thus, a solution of one part in a thousand forms a useful injection in chronic gonorrhœa; in purulent ophthalmia a 1 per cent. solution is considerably used, whilst stronger solutions may be employed for painting on chronic ulcers to stimulate healing.

One objection to the local use of silver nitrate is that it is precipitated by chlorides, and much of its action is thus destroyed: for this reason a large number of new silver compounds have been introduced to supersede it. Argonin is a combination of casein and silver, soluble in water, but not precipitated by proteids or chlorides. Protargol is another combination with protein, of doubtful composition. Credé has advised the use of an ointment composed of colloidal silver, and some body such as lard. Clinical and experimental evidence shows that these have no advantage over silver nitrate.

When taken internally in sufficient doses silver salts produce acute gastro-enteritis, and death from collapse. If the administration is in smaller doses, but over prolonged periods, a minute amount is absorbed, and, after circulating in the blood, is deposited in a granular form in various parts of the body as an organic compound

of silver having a bluish-grey colour. These granules are chiefly found in the connective tissues, to which they impart a characteristic appearance. The condition begins with a dark discoloration of the mouth and gums, and often there is a dark line at the margin of the teeth and gums resembling that in lead poisoning. The skin acquires a peculiar bluish-slate colour, from deposition of pigment in the corium, and in well-defined cases the mucous membrane of the conjunctiva is also involved. This pigmentation or argyria, as it is called, affects to a greater or less extent all the connective tissue throughout the body, but it is not usually accompanied by any noxious symptoms. When once developed it is impossible to get rid of it, as the only salt at present known in which it is at all soluble is potassium cyanide. Argyria has been known to occur after the prolonged local application of silver to the urethra, vagina, and eye.

Silver taken by the mouth is discharged in the fæces as the sulphide. A minute amount is absorbed and retained permanently; some is, however, excreted by the rectum.

In man silver never gives rise to poisonous symptoms other than gastro-enteritis. If a soluble salt of silver, which does not coagulate albumen, is injected into the veins of animals, nervous symptoms are slowly induced; they consist of convulsions followed by paralysis of the hind-limbs and, later, by medullary paralysis. These effects are of little practical importance, since sufficient silver is never absorbed by man at any one time to allow of their being produced. Silver is now almost solely employed as a local astringent on the skin and mucous membranes, including the alimentary canal. Formerly it was used internally in epilepsy, but, as it is absorbed so very slowly, it is difficult to see how it could have produced any effect in these cases.

MATERIA MEDICA

1. **Argenti Nitras.**—$AgNO_3$. Lunar caustic. Dose, $\frac{1}{4}$ to $\frac{1}{2}$ gr. (16 to 30 mgrms.).

2. **Argenti Nitras Induratus.**—Toughened caustic. A mixture of $AgNO_3$ 19 parts, and KNO_3 1 part.

3. **Argenti Nitras Mitigatus.**—Mitigated caustic. A fused mixture of $AgNO_3$ 1 part, and KNO_3 2 parts.

ALUMINIUM

The salts of aluminium are local astringents and antiseptics. Potash alum precipitates albumen and gelatin, and the albuminate is soluble in excess of the proteid. It is employed almost entirely as an astringent to mucous membranes. Thus, it may be used for painting on the tonsils, as a gargle in tonsillitis, or as an astringent in conjunctivitis. When it is applied locally, its astringent action also renders it styptic and antiseptic.

Taken internally, it is astringent to the mucous membrane of the alimentary canal and induces some constipation. Large doses give rise to gastro-enteritis.

Aluminium is not absorbed, but the injection of a double salt, such as the sodium aluminium tartrate, into animals produces changes in cell-metabolism, and affects the central nervous system. The former effect is characterised by loss of weight and fatty degeneration, and the latter by tremors, convulsions, and diminution of sensations. These changes are not produced until one or two weeks after the injection.

Numerous preparations of aluminium have recently been introduced into medicine: as examples we may cite **aluminium-aceto-tartrate,** which is a good antiseptic and easily soluble in water. It is a milder astringent than alum. **Alumnol** is aluminium-naphthol-sulphonate. It precipitates albumen, and is therefore astringent and antiseptic.

MATERIA MEDICA

1. Alumen Purificatum.—Alum. A sulphate of aluminium and potassium (potassium alum), $Al_2(SO_4)_3,K_2SO_4,24H_2O$, or a sulphate of aluminium and ammonium (ammonium alum), $Al_2(SO_4)_3,(NH_4)_2,SO_4,24H_2O$. **Dose, 5 to 10 grs.** (3 to 6 decgrms.).

PREPARATION

Glycerinum Aluminis.—16 per cent.

2. Alumen Exsiccatum.

3. Kaolinum.—Kaolin. Native aluminium silicate soluble neither in water nor dilute acids. Used as an excipient for pills containing phosphorus and silver nitrate: also used as a variety of fuller's earth.

COPPER

The soluble copper salts have a typical astringent action on the mucous membranes. They precipitate albumen, and large doses of the sulphate or nitrate produce corrosion. The sulphate is applied locally as a mild caustic and to destroy exuberant granulations. In weak solution it is sometimes employed to check excessive discharges from mucous membranes, such as may occur in ophthalmia or chronic gonorrhœa.

When taken internally copper salts cause nausea and vomiting with their attendant symptoms. The action is entirely local on the stomach, for much larger doses are required subcutaneously to produce the same effect; and moreover, the injection takes longer to induce emesis. Both these facts prove that the emesis is excited locally.

Large amounts of the drug given by the mouth produce corrosion of the gastric epithelium, with violent pain, vomiting, and purging,

and ultimately death from collapse. Some degree of tolerance to copper salts, as to any other corrosive poison, can be attained. There is no evidence that man is ever affected with chronic copper poisoning, so that the use of copper cooking-vessels, and the employment of minute amounts of copper to "improve" the appearance of peas, may not be so harmful as might be supposed.

If one of the double salts of copper is injected into the circulation of an animal the special effect of the drug can be determined. This consists chiefly in complete paralysis of the central nervous system. This metal is absorbed in minute quantities, and is invariably found in the tissues of animals and plants. It seems, like other metals, to be stored up in the liver, spleen, and kidneys.

Copper, then, is not very toxic after physiological absorption into the mammalian system, and this is probably because it exists in some non-toxic combination; on the other hand, combinations not so prepared in the cell laboratory are some of the most toxic drugs known. Even the traces present in water distilled from copper vessels will kill tubifex and tadpoles. And the same water used to make up Ringer's solution kills the mammalian heart when perfused by Langendorff's method.

Copper sulphate is used as an emetic, especially in poisoning by phosphorus. The phosphorus is oxidised to phosphate by the copper sulphate, and any unchanged phosphorus combines with the reduced copper, forming insoluble copper phosphide.

MATERIA MEDICA

Cupri Sulphas.—$CuSO_4.5H_2O$. **Dose, ¼ to 2 grs.** (60 to 120 mgrms.) as an astringent; **5 to 10 grs.** (3 to 6 dcgrms.) as an emetic.

ZINC

The action of zinc bears many resemblances to that of copper. The soluble salts form with proteids a typical insoluble albuminate, to which the metal owes its astringent properties. A solution of the sulphate or acetate is commonly employed for this purpose in chronic inflammations, and is also used as a 1 per cent. solution, or stronger, in leucorrhœa, gleet, and as an eye-wash. Zinc sulpho-carbolate is employed externally like the sulphate as an astringent and antiseptic. Zinc chloride is much more astringent than the sulphate. Formerly it found a very large use as a paste with flour or gypsum to destroy malignant growths, the flour or gypsum being necessary to prevent the action from extending too far owing to the deliquescent nature of the salt. A solution of zinc chloride having a specific gravity double that of water was at one time in general use as an antiseptic and disinfectant under the title of Burnett's disinfecting fluid. The car-

bonate, oxide, and oleate are employed in ointments as mild astringents upon excoriated or slightly ulcerated surfaces.

The salts of zinc, when taken internally, have a metallic taste and produce nausea and vomiting. Larger quantities give rise to intense pain in the abdomen, purgation, and death from collapse. These effects are, of course, most marked with the chloride, and least with the insoluble preparations like the carbonate and oxide.

Zinc salts are not absorbed from the alimentary canal in amounts sufficient to produce noticeable specific effects. The double salts of zinc, when injected into the circulation of mammals, give rise to vomiting, diarrhœa, muscular tremors, and ultimately to paralysis of the central nervous system. Chronic poisoning from zinc has been observed in smelters who inhale the fumes; the symptoms closely resemble those of lead, and consist of derangements of the alimentary canal, colic, and peripheral neuritis.

Zinc salts, especially the sulphate and carbonate, were formerly used in cerebral affections like chorea and epilepsy, but there is no pharmacological evidence that zinc has any central sedative action.

When gradually increasing doses of the sulphate are given, a small degree of tolerance is soon attained. Poisoning is rare, and should be treated like copper poisoning by tannic acid, white of egg, milk, and demulcents.

MATERIA MEDICA

1. **Zinci Sulphas.**—$ZnSO_4 7H_2O$. Readily soluble in water. **Dose, 10 to 30 grs.** (6 to 20 dcgrms.) as an emetic.

PREPARATION

Unguentum Zinci Oleatis. Equal weights of zinc oleate and soft paraffin.

2. **Zinci Chloridum.**—$ZnCl_2$. Freely soluble in water.

PREPARATION

Liquor Zinci Chloridi.—Treat zinc (1 lb.) with hydrochloric acid (44 oz.) and add water. Sp. gr. 1.53.

3. **Zinci Oxidum.**—ZnO. **Dose, 3 to 10 grs.** (2 to 6 dcgrms.).

PREPARATION

Unguentum Zinci.—Zinc oxide, 3; benzoated lard, 17.

4. **Zinci Carbonas.**—$ZnCO_3(ZnH_2O_2)_2.H_2O$.

5. **Zinci Acetas.**—Zinc acetate. $Zn(C_2H_3O_2)_2 3H_2O$. **Dose, 1 to 2 grs.** (6 to 12 ctgrms.).

6. **Zinci Oleostearas.**

7. **Zinci Valerianas.**—**Dose, 1 to 3 grs.** (6 to 20 ctgrms.).

CHROMIUM

Two preparations of chromium are used in medicine, chromic acid and potassium bichromate. They are both excellent oxidising agents, and are employed as antiseptics and disinfectants.

Chromic acid coagulates albumen and is used as a caustic. It is sometimes used to destroy granulations and excrescences, and to wash out poisoned wounds.

Potassium bichromate has lately been employed as a mild astringent in dyspepsia in doses of $\frac{1}{12}$ gr. A saturated solution is occasionally used as a caustic for superficial growths.

Chromium salts are readily absorbed, but in cases of poisoning death is caused by local gastro-enteritis followed by collapse. In the manufacture of bichromate of potash the workmen are peculiarly liable to sores on the skin and septum nasi: these ulcers always follow some previous abrasion.

MATERIA MEDICA

1. **Acidum Chromicum.**—CrO_3.

PREPARATION

Liquor Acidi Chromici.—25 per cent.

2. **Potassii Bichromas.**—$K_2Cr_2O_7$. **Dose,** $\frac{1}{10}$ **to** $\frac{1}{5}$ **gr.** (6 to 12 mgrms.).

MANGANESE

The only official salt is potassium permanganate, which owes its action to its capacity for parting with oxygen to albumen or other organic matter. It is therefore used as a disinfectant and deodorant; but its power is limited, because when it yields up its oxygen it becomes inert. Concentrated solutions irritate mucous membranes, and may even induce gastro-enteritis.

Permanganate is used internally as a dilute solution for washing out the stomach in cases of alkaloid poisoning, especially morphine. It is also valuable as a local remedy in snake-bite, for it destroys the poison when it comes into direct contact with it.

Condy's Fluid is a strong solution of impure permanganate.

MATERIA MEDICA

Potassii Permanganas. Dose, 1 to 3 grs. (6 to 20 ctgrms.).

PREPARATION

Liquor Potassii Permanganatis.—1 per cent. solution. **Dose, 2 to 4 drs.** (7 to 15 mils).

CHAPTER XXX

ANTHELMINTICS AND DRUGS USED TO KILL PARASITES

"ANTHELMINTIC" is the name given to drugs which are employed to get rid of worms. Such drugs possess few features in common; but, like the vegetable purgatives, they are absorbed only with difficulty, so that they can exert their poisonous effects on the parasite in the alimentary canal without seriously affecting the host. Active purgatives alone may get rid of some of the parasites from the alimentary canal by increasing the peristalsis, but rarely of all unless an anthelmintic has been previously administered; the effect of the latter is either to lower the vitality of the worms, thus rendering them unable to withstand the increased peristalsis, or to cause them to migrate to the large intestine.

Anthelmintics do not usually kill the parasite, and when the drug has disappeared from the intestine the worms soon recover their former condition. Hence, soon after the administration of the anthelmintic a brisk purgative or vermifuge must always be administered to expel the worm. It is better to administer anthelmintics when the bowels are empty: a dose of castor oil is given at night and the anthelmintic first thing in the morning, followed again by a brisk purgative some hours later.

The worms with which one has most commonly to deal in this country are the following:—

		Anthelmintics
Tape-worm	Tænia mediocanellata Tænia solium Bothriocephalus	Filix mas, granatum, cusso, or terebene.
Round worm	Ascaris lumbricoides	Santonin.
Thread-worm	Oxyuris vermicularis	Enemata of salt solution, quassia, or iron salts.

A number of other drugs, which are generally protoplasmic poisons and not very readily absorbed, have also been employed as anthelmintics. Such are thymol, naphthol and other coal-tar products, but, as a rule, if these are given in big enough doses for their purpose, a sufficient amount is absorbed to produce toxic symptoms in the host. Thread-worms which have their habitat in

the rectum are best got rid of by means of enemata ; an infusion of quassia or a simple salt solution will generally be found quite effective for this purpose.

Most anthelmintics in large doses produce gastro-intestinal irritation, and, as with the more irritant vegetable purgatives, death from collapse may result. Under certain conditions absorption occurs, and the specific effect of the particular drug is produced.

SANTONIN

Santonin ($C_{15}H_{18}O_3$) is a crystalline principle obtained from santonica, the dried flowering heads of *Artemisia maritima*. It is the anhydride of a monobasic acid, and is insoluble in water, but soluble salts can be formed by warming it with alkalies.

Action.—Santonin is the most successful anthelmintic for getting rid of the round worm. It does not kill the worm, for it is expelled alive; and it does not even kill it when a ½ per cent. solution of santonin in oil is allowed in direct contact with it outside the body, although it increases the movements of the animal and apparently renders it uncomfortable. How it acts is not definitely known, but it possibly either lowers its vitality so that it no longer resists the movements of peristalsis or it causes it to migrate to the lower gut : in either case it is expelled by the after-purgative. The drug should always be accompanied or followed by a purge, castor oil being the one generally used for this purpose.

Santonin also gets rid of thread-worms, but has no action on tæniæ. It has a slightly bitter taste in the mouth, passes through the stomach unchanged, but some is absorbed as sodium santonate in the small intestine. Santonin, however, is a very insoluble body, so that most of it reaches the intestines to affect the round worm. The principal drawback to the use of this drug is its too ready absorption, as shown by the " yellow vision " and the intensely yellow urine. It is even possible, under suitable conditions, for so much santonin to be absorbed as to poison the patient and to leave the worms unaffected.

Effect on Sense-organs.—The specific effects of santonin show themselves on the sense-organs and the central nervous system.

After taking a few grains, the " yellow vision " is developed within an hour. All illuminated objects appear to have a yellowish tinge, which is sometimes preceded by the presence of a faint blue colour. This blue tinge is due to chromatic aberration, and may be obtained with any drug which, like santonin, dilates the pupil. People under the influence of santonin lose their appreciation for difference of colour at the violet end of the spectrum, being unable to distinguish between violet and black; whilst at the yellow end the acuity of vision is exaggerated. It has been suggested that these results may be due to stimulation, followed by paralysis of those fibres

by which violet rays are perceived, but all the evidence points to a central action.

Other senses, taste, smell, and hearing, have in a few cases been deranged.

Effect on the Central Nervous System.—The absorption of small doses of santonin gives rise to vague cerebral symptoms, such as headache, vertigo, nausea and vomiting. With larger doses epileptiform convulsions occur. These begin with twitchings of the muscles of the face and head, and are soon followed by a typical tonic convulsion with opisthotonus, and, later, by clonic convulsions. This attack is followed by an interval of rest, except for some apparently spontaneous contractions of the muscles, and is succeeded by fits following one another in a series, the whole closely resembling an ordinary epileptic fit. In the early stages these convulsions may be arrested by chloroform or by section of the cord, and they are therefore probably cortical; and in further support of this is the fact that the fit begins in the head region, and that the convulsions are clonic in nature. Death results from respiratory failure. After very large doses of santonin the cord is also affected, and convulsions, resembling those produced by strychnine, may be induced even when the medulla and brain are destroyed.

Excretion.—Such santonin as is absorbed into the system is excreted by the kidneys either as the sodium salt or as an oxysantonin. The urine, if acid, is turned intensely yellow, but if alkaline or if alkali is added to the acid urine it assumes a purplish colour. A similar coloration is induced by chrysophanic acid, one of the anthraquinone derivatives contained in senna. If the urine is shaken with ether the emodin and chrysophanic acid are dissolved out, but not the santonin colouring matter.

Santonin sometimes produces irritation of the kidney, with painful micturition and hæmaturia.

MATERIA MEDICA

Santoninum.—Feebly soluble in cold water, and easily in chloroform. It forms santonates with alkalies. **Dose, 1 to 3 grs.** (6 to 20 ctgrms.). For a child one year, ½ gr.

PREPARATION—**Trochiscus Santonini.**—1 gr. in each.

FILIX MAS (Male Fern).

The rhizome of *Aspidium filix mas* contains a variable amount, 5 to 8 per cent., of filicic acid; but old species, those kept more than one year, often contain only a trace, because the acid changes to the anhydride "filicin," which is inactive. A second active substance, aspidin, is also present, sometimes to 2 or 3 per cent., but sometimes only traces are to be found. These two bodies are not present in quantity together; if one is present in considerable amount the other is in traces only, and *vice versa*. The presence of the one or the other appears to be determined by habitat, the conditions of growth of the plant, etc. Both are

anthelmintic, and it is not yet settled whether an oleo-resin, containing principally aspidin, or one rich in filicic acid is the better therapeutically.

Other constituents of the drug are a fixed oil and a volatile oil. Filmaronic acid is yet another body stated to be the active principle and which decomposes into filicic acid and aspidin. All these active constituents, representatives of which are present in most ferns, are compounds of butyric and isobutyric acid with phloroglucinol or its homologues.

Action.—Filix mas is used clinically as a remedy for tæniæ, to all varieties of which it is a direct poison. One or two drachms of the liquid extract should be administered early in the morning, after a dose of castor oil at bedtime. About twelve hours later another purge must be given to clear out the worm, the head of which must also be passed if a complete cure is to be assured. It is generally suggested that oily substances, such as castor oil, should be avoided during this treatment, as they tend to dissolve filicic acid and facilitate absorption.

In very large doses filix behaves as a violent irritant to the alimentary canal, and gives rise to vomiting, purging and griping, acute abdominal pains, and ultimately death from collapse. Post-mortem the ordinary signs of acute gastro-enteritis are found.

It is absorbed very slowly, but sometimes sufficient drug is taken up to produce specific effects, which are characterised by muscular weakness and sometimes by twitching of the muscles, mental confusion, and a tendency to sleep. Temporary blindness has also been noted, although the fundus of the eye presents quite a normal appearance. A destruction of the red blood-cells with resulting jaundice sometimes occurs.

Filicic Acid.—If 0.5 gram of filicic acid is given to a rabbit by the stomach, it first acts as an irritant to the gastro-intestinal canal. After absorption strychnine-like convulsions are produced, and, should the animal recover from these, the ultimate excretion of the drug by the kidney may lead to acute nephritis.

If dogs are given 0.2 gram per diem they develop amaurosis, which may leave the animals permanently blind. In man 5 to 10 grams give rise to a sort of general intoxication and amaurosis.

It is toxic to the smooth muscle of invertebrates, and it has been suggested that it paralyses the muscle of tæniæ.

Pure filicic acid has not a very strong effect on tæniæ: it is possible that the presence of the volatile oil aids the activity of the acid by rendering it more soluble, or that the active constituent is due to a minute amount of some other body.

Aspidin produces no effect in mammals unless the drug be injected directly into the circulation, when strychnine-like convulsions appear; and ultimately death is produced from medullary paralysis.

The poisonous effects of filix when it is administered by the mouth must, therefore, be the result of filicic acid, since no aspidin is absorbed.

MATERIA MEDICA

Filix Mas. PREPARATION—**Extractum Filicis Liquidum.**—Oleo-resin. (Must contain not less than 20 per cent. of filicin.) **Dose, 45 to 90 m.** (3 to 6 mils) in an emulsion with mucilage.

COUSSO

Cousso consists of the panicles of the female flowers of *Brayera anthelmintica*. It contains kosotoxin, the active principle, which is a strong muscular poison, protokosin (an inactive substance), a bitter acrid resin, some tannin, and a little volatile oil. Kosotoxin is soluble in alcohol and alkaline fluids, but is insoluble in water. It is chemically allied to filicic acid.

Action.—Cousso acts like male fern and is a powerful protoplasmic poison, but it is less certain in its effect. It apparently kills by direct contact, for the worm is expelled dead, and often in small fragments. A dose of ½ to ½ oz. as a fresh infusion should be drunk without straining. Large doses may give rise to gastro-intestinal irritation.

Kosotoxin, injected into frogs, has a curare-like action on nerve-endings, and it ultimately weakens and paralyses striped muscle, including cardiac. In mammalia the muscle-fibre is similarly affected: death is produced by medullary paralysis.

As an anthelmintic it should be preceded by a purge; the drug is then taken on an empty stomach and followed in a few hours by a further brisk purge, although the natural action of the drug may render this unnecessary.

Both kosotoxin and filicic acid belong to the strychnine curare group. They are less effective than strychnine in augmenting reflexes, and less effective than curare in producing paralysis of the motor nerves.

MATERIA MEDICA

Cousso. Dose, ¼ to ½ oz. (8 to 16 grms.) in fresh infusion.

PELLETIERINE

Pomegranate root is from *Punica granatum*. It contains four alkaloids — pelletierine, isopelletierine, methyl-pelletierine, and pseudo-pelletierine. The first two only are active; all are liquid but the last. There may be as much as 3 per cent. of alkaloid in the root-bark, but rarely more than 0.5 per cent. in the stem-bark. Commercial pelletierine is a mixture of the two active alkaloids. The bark also contains about 20 per cent. of tannin.

Action.—If Tænia serrata (tape-worm of the cat) is placed in a 0.01 per cent. solution of pelletierine, it loses its power of movement in about five minutes, but will, nevertheless, recover if it is then taken out of the solution; if, however, it is left longer than ten minutes it dies. This effect corresponds to that produced on the parasite when the drug is administered to patients.

The best way to administer this drug is to give 2 oz. of the fluid decoction every two hours for four doses, and follow by a brisk purge; it is an extremely objectionable drug to take. Granatum has also been employed as an astringent in diarrhœa on account of the large amount of tannin it contains.

Large doses produce nausea, vomiting, colic, and diarrhœa. In frogs injections of pelletierine at first increase the reflexes, and subsequently paralyse the motor nerve-endings like curare; they produce a veratrine-like action on striped muscle. In mammalia and man there is an increase of the reflexes, followed by a sense of weakness in the limbs and cramps in the leg-muscles; later, cerebral symptoms, such as vertigo, drowsiness, and coma, may come on. Ocular disturbances as in filix, dilatation of the pupil, amaurosis, and retinal congestion have also been descried.

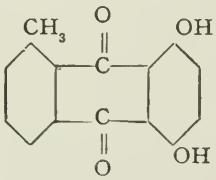
Pelletierine.—The sulphate is a viscid liquid soluble in water, and the tannate is a powder insoluble in water. Both are administered in doses of from 5 to 8 grs. as anthelmintics. The tannate is probably the better preparation, as the tannic acid tends to prevent its absorption in the stomach.

MATERIA MEDICA

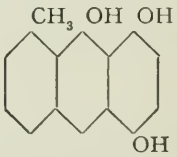
Pelletierinæ Tannas. Dose, 2 to 8 grs. (12 to 50 ctgrms.).

ARAROBA AND CHRYSAROBIN

Araroba, Goa powder, or crude chrysarobin is a substance found in cavities in the trunk of *Andira araroba*. It should yield not less than 50 per cent. of chrysarobin. Now chrysarobin on oxidation gives chrysophanic acid, and the so-called chrysarobin of the Pharmacopœia may consist of a mixture of true chrysarobin and



Chrysophanic acid.



Chrysarobin.

chrysophanic acid, both of which are strongly antiseptic and irritant. An ointment of chrysarobin is valuable, therefore, in the treatment of skin diseases which are due to fungi; and it is also employed as a stimulant and mild irritant in cases of chronic skin

disease, such as psoriasis. An objection to the use of this drug is the fact that it stains linen with which it comes in contact. It is probable that the beneficial action in chronic skin diseases such as psoriasis is due to an oxidation taking place upon the skin in which the oleic acid secreted by the glands is concerned.

Internally chrysarobin has the same action as chrysophanic acid. Doses of from 5 to 20 grs. induce vomiting and purging. Like chrysophanic acid some of the drug is absorbed, since the urine assumes an intensely yellow colour, and this excretion by the kidney is associated with pain in the back. The bulk of the drug is unabsorbed and passes out of the body with the fæces.

Chrysarobin, like pyrogallol, rapidly absorbs oxygen.

MATERIA MEDICA

Araroba.—Contains about 50 per cent. chrysarobin.

Chrysarobin. PREPARATION. **Unguentum Chrysarobini.**—4 per cent.

SULPHUR AND THE SULPHIDES

Sulphur is a completely inert substance, but under certain conditions it is converted into sulphide, and may then be regarded as exerting a weak sulphide action.

When it is applied to the skin, the cutaneous secretions convert a small proportion to sulphides, and these exert a very mild irritant effect: as fresh sulphide is constantly though very slowly being formed, a mild degree of stimulation lasting over a prolonged period is obtained. Sulphur as an ointment is much used as an application to the skin for the purpose of destroying the insect of itch and various fungal growths. If the drug is applied to an ulcer or to an inflamed area of skin a larger proportion of sulphide is formed, leading to a much more severe irritation, and sometimes even to destruction of tissues. The constant irritation of a sulphur ointment even to a healthy skin will in time give rise to inflammation. In such cases a small amount of absorption generally occurs, and is easily recognised by the characteristic smell of sulphuretted hydrogen in the breath.

Sulphur passes through the stomach unaltered. In the small intestine and all through the large intestine it is partly transformed to sulphuretted hydrogen, which normally stimulates peristalsis. Sulphur softens the stools, but produces no marked purgative action; even very large doses give rise to relaxation only, and never to colic. The explanation of this fact is that the amount of sulphide formed is not in any way proportional to the sulphur taken. Possibly, also, sulphur acts physically, somewhat like bismuth, and forms a coating on the walls of the gut, which protects the mucous membrane from excessive stimuli.

The greater part of the sulphur is excreted unchanged in the fæces. A small proportion is absorbed as alkaline sulphide, and this is

oxidised in the body and excreted mainly as sulphate in the urine. The absorption as sulphide depends to some extent on the mode of administration: if sublimated sulphur is administered, only 5 to 10 per cent. can be detected in the urine as sulphate, whilst if milk of sulphur is given a much larger quantity (30 to 50 per cent.) is said to be so excreted. Small quantities of sulphur are also excreted from the lungs, giving a disagreeable odour to the breath, and acting as a slight expectorant. Traces of sulphur compounds are excreted from the skin, and the irritation of these may sometimes produce a rash. The perspiration is increased, has a disagreeable odour, and silver articles worn about the body may be blackened.

Sulphur circulates in the blood as alkaline sulphide, but as a general rule sufficient is not absorbed to produce the specific effects of the sulphides. To produce the specific action the sulphides themselves must be administered. If a subcutaneous injection of sulphide of sodium is made into a dog, the brain—especially the motor area and the medulla—is stimulated. This is shown at first by excitement, and later by the production of convulsions, which are abolished if the cord is severed from the medulla. Stimulation of the medulla is shown by the usual signs—deeper respiration, which is still evident after section of the vagi, and by vaso-constriction. The stimulation is followed by paralysis, and death ensues from respiratory failure.

Frogs are very susceptible to sulphides: a small injection first leads to depression of all reflexes; this is followed, as in the case of morphine, by a second stage of hyperexcitability, sometimes accompanied by strychnine-like convulsions and opisthotonus; this stage may last for weeks.

Sulphides are, of course, very active reducing agents. If they are added to a little drawn blood they reduce the oxyhæmoglobin, and form with the hæmoglobin a peculiar sulphide compound having a characteristic spectrum. This compound is not found in the body of the living mammal (Fig. 69).

Potassa Sulphurata and Calx Sulphurata

Such bodies are easily decomposed: even so weak an acid as carbonic will liberate sulphuretted hydrogen, and hence such compounds are not formed in the alimentary canal. Externally they possess all the actions of sulphur, but if at all concentrated they behave as powerful irritants. If from 1 to 10 grs. are administered to a man the effect will be much the same as if a dose of sulphur had been taken, except there is likely to be some irritation of the stomach from the liberation of H_2S. With big doses all the symptoms of poisoning by sulphuretted hydrogen may be seen.

MATERIA MEDICA

1. **Sulphur Sublimatum.**—Flowers of sulphur. **Dose, 20 to 60 grs.** (12 to 40 dcgrms.).

Preparation

Unguentum Sulphuris.—10 per cent.

1. **Sulphur Præcipitatum.**—Milk of sulphur. **Dose, 20 to 60 grs.** (12 to 40 dcgrms.).

2. **Confectio Sulphuris.**—Also contains acid potassium tartrate. **Dose, 60 to 120 grs.** (4 to 8 grms.).

Preparation

Trochiscus Sulphuris.—Contains 5 grs. sulphur.

3. **Potassa Sulphurata.**—Liver of sulphur. A mixture of potassium trisulphide, K_2S_3, and thiosulphate, $K_2S_2O_3$. It is soluble in water and some H_2S is liberated.

4. **Calx Sulphurata.**—Sulphurated lime. A mixture containing not less than 50 per cent. of calcium sulphide, with calcium sulphate and carbon. **Dose, $\frac{1}{4}$ to 1 gr.** (16 to 90 mgrms.) in pill.

BORACIC ACID AND BORAX

These substances are used on account of their antiseptic action. Their effect is, however, feeble, as even a 4 per cent. solution, whilst preventing the growth of bacteria for the time it is in contact with them, does not affect their subsequent development. Boric acid is very largely used to preserve milk, butter, and animal food. Animal tissue will keep eight days in the presence of a $\frac{1}{2}$ per cent. solution of the acid, and milk can be preserved from fermentation for several days in the presence of a 0.2 per cent. Solutions of the acid are commonly used to wash out cavities after operations; and in the solid form it is employed as a dusting powder or for application to simple ulcers about the mouth and tongue.

Borax is also used as a preservative for milk, but its use is improper as it impairs the coagulability of casein.

Taken internally boric acid and borax are easily absorbed and are excreted in the urine, and to a slight extent in the milk and saliva, elimination being generally not complete within twenty-four hours.

The specific effects have lately received considerable attention on account of the symptoms of poisoning said to be produced when they are used as food preservatives. These symptoms consist of loss of appetite, general signs of mild gastro-enteritis (nausea, vomiting, and mild diarrhœa), nervous prostration, and muscular weakness. There are also cutaneous lesions, of which the commonest is a scaly dermatitis: more rarely bullæ, petechiæ, loss of hair, and dryness of the skin have been observed. The amounts actually

present in food may certainly be injurious to health, but the action depends upon the dose and the individual idiosyncrasy of the patient. Renal disease certainly increases susceptibility to poisoning. Borax and boracic acid given daily to children in very small doses have been reputed not in any way to affect health, metabolism, or intestinal putrefaction as measured by the amount of aromatic sulphate in the urine.

One gram taken daily in the food certainly exerts a deleterious action, augmenting combustion, so that the patient rapidly loses weight. A healthy man placed on 5 grs. of boric acid daily lost 7 lb. in a fortnight. One reason for this toxic action is its slow excretion, so that the drug tends to cumulate.

MATERIA MEDICA

Acidum Boricum, H_3BO_3. Dose, 5 to 15 grs. (3 to 10 decgrms.).

PREPARATIONS

1. **Glycerinum Acidi Borici.**—30 per cent.
2. **Unguentum Acidi Borici.**—10 per cent.

Borax Purificatus, $Na_2B_4O_7$. Dose, 5 to 15 grs. (3 to 10 decgrms.).

PREPARATIONS

1. **Glycerinum Boracis.**
2. **Mel Boracis.**

FORMALDEHYDE

Formic aldehyde is a colourless gas irritating to the conjunctiva and mucous membranes, and which is used in watery solution. Combined with ammonia it forms hexamine, from which the aldehyde can be again obtained by acids. The value of hexamine as a urinary antiseptic depends on this fact. Formic aldehyde is used in the gaseous form to disinfect rooms, and for this purpose is obtained by heating polymerised formaldehyde with moisture. It causes no injury to metals or fabrics.

Formic aldehyde is a most important germicide and possesses considerable penetrating power, which facilitates its action on micro-organisms. A solution of 0.2 per cent. kills most bacteria and cocci ; it also coagulates proteins. It is used as a general antiseptic, such as in the treatment of wounds; to paint on infected areas, diphtheria and ringworm; to disinfect excreta.

Taken internally formaldehyde is very irritant, but is not poisonous after absorption, since it is oxidised to carbonic acid except a trace, which is excreted in the urine as formic acid.

MATERIA MEDICA

Liquor Formaldehydi.—36 to 38 per cent. formalin.

Liquor Formaldehydi Saponatus.—20 per cent. of the liquor with soft soap. Employed for surgical cleansing, but is too irritant for general use.

HYDROGEN PEROXIDE

Hydrogen peroxide (H_2O_2) owes its efficacy to the liberation of free oxygen. Many bodies, including all forms of living matter, bring about this change. It is a useful disinfectant, its advantages being that it is non-poisonous and scarcely irritant; the products of its decomposition are innocuous, and it does not precipitate albumen. If it is injected into the circulation, it is poisonous to the higher animals by forming oxygen embolisms, and it may be dangerous even to wash out serous cavities if more oxygen is absorbed than the blood can dispose of. Various proprietary preparations contain H_2O_2. "Sanitas" owes most of its disinfectant properties to this substance. "Golden hair wash" produces its bleaching action by this drug. "Menthoxol," "camphoroxol," and "naphthoxol" consist of a 3 per cent. solution of H_2O_2 with menthol, camphor, and naphthol respectively. When used on suppurating surfaces and wounds it has little germicidal action, for it is decomposed by catalase in all body tissues: in these cases it probably acts by the destruction of poisonous products.

SODIUM PERBORATE

Sodium perborate, $NaBO_3$, $4H_2O$, is usually met with as a white powder. A solution possesses the oxidising properties of an alkaline solution of hydrogen peroxide. On warming, oxygen is rapidly evolved. It is employed as an antiseptic, its activity being due to liberation of oxygen by contact with catalysers or organic matter in the presence of moisture. It may be used as an application to wounds and ulcers, in solution (2 per cent.).

MATERIA MEDICA

Liquor Hydrogenii Peroxidi. Dose, ½ to 2 drs. (2 to 8 mils). A solution of about 3 per cent. Very unstable.

CHAPTER XXXI

EMOLLIENTS, DEMULCENTS—SWEETENING AND COLOURING AGENTS

EMOLLIENTS are substances which soften and relax, while demulcents protect and soothe the parts to which they are applied. There is no sharp line of demarcation between the two groups, some substances, such as olive oil, partaking of the properties of both; but, as a general rule, the term emollient is restricted to substances to be applied to the skin, and demulcent to those applied to the mucous membrane. The following is a list of the most important members :—

Emollients.	Demulcents.	Sweetening Agents.	Colouring Agents.
Lard.	Gums.	Cane-sugar.	
Fats, such as suet and lanoline.	Starch.	Milk-sugar. Glucose.	Coccus.
Olive oil, oleic acid.	Gelatin.	Syrups.	Red sandal-wood.
Almond oil.	Linseed.	Honey.	Red poppy petals.
Linseed oil.	Liquorice.	Saccharin.	
Spermaceti.	Sweet almonds.		
	* * *		
Beeswax.	Collodium.		
Paraffins.	Cotton-wool.		
Soaps.	Acetone.		
Glycerin.			

FATS, FIXED OILS, WAX, SOAP, AND PETROLEUM

FATS

The fats used in medicine are derived from both animal and vegetable sources. With few exceptions the basic radicle is the same for all fats and fixed oils, viz. glyceryl (C_3H_5). The acid radicles are many, the chief being palmitic, stearic, and oleic, each fat containing three or four such radicles combined with the glyceryl group. Thus, we have :—

$C_3H_5(C_{18}H_{33}O_2)_3$ = olein (glyceryl oleate).
$C_3H_5(C_{16}H_{31}O_2)_3$ = palmitin.
$C_3H_5(C_{18}H_{35}O_2)_3$ = stearin.

Adeps (lard) is the purified abdominal fat of the hog. It consists of about 40 per cent. stearin and palmitin, and about 60 per cent. olein. When it is exposed to the light oxidation and hydrolysis, with resulting rancidity, are apt to occur. The chemical changes are brought about by organisms.

Adeps benzoatus.—Prepared by adding benzoin to melted lard. The benzoic acid inhibits the growth of organisms, and the lard does not become rancid.

Adeps lanæ (wool-fat) is the purified cholesterin-fat of the wool of sheep. It has a varying composition, its most prominent constituents being cholesterin, iso-cholesterin, and their esters, with a small amount of ordinary glycerides. It does not become rancid.

Adeps lanæ hydrosus (lanoline or hydrous wool-fat), prepared by triturating wool-fat with water. It makes an excellent basis for ointments.

Sevum præparatum (prepared suet) consists of the internal fat of the sheep's abdomen purified by melting and straining. It contains 70 to 80 per cent. of stearin and palmitin, with only 20 to 30 per cent. olein, and hence its high melting-point.

Sevum benzoatum.

Acidum oleicum constitutes the major part of olive and almond oils and a considerable portion of tallow and lard. In the common oils and fats it is associated with the glyceryl esters of stearic and palmitic acids. The oleates of mercury, lead, and zinc do not ionise.

Oleum olivæ is obtained by expression from the pericarp of the ripe fruit of *Olea Europæa*. The chief constituent is glyceryl oleate (olein), over 70 per cent. Palmitin, arachin, cholesterin, and free fatty acid are also present. Used as a purgative and for biliary colic.

Oleum amygdalæ (almond oil) is obtained by expression from both bitter and sweet almonds. Sweet almonds contain about 45 per cent. of fixed oil, and bitter almonds about 38 per cent. The oil consists of 76 per cent. olein ; the rest is a mixture of palmitin and stearin.

Oleum lini (linseed oil) is prepared from dry ripe linseed by expression. It consists chiefly of the glyceryl ester of linoleic acid with small quantities of the glyceryl esters of oleic, stearic, palmitic, and myristic acids. When the oil is exposed to the air a varnish is formed by the linolein absorbing oxygen. It is the best drying oil known.

Oleum theobromatis.—Oil of theobroma or Cacao butter is obtained by expression from the seeds of *Theobroma cacao*. Glycerides of stearic, palmitic, and lauric acids form its chief constituents. It is used for making suppositories, because it is a hard solid which can be moulded at ordinary temperatures and yet melts below the temperature of the body.

Oleum ricini (castor oil) and **Oleum tiglii** (croton oil) are considered under Purgatives.

Waxes

The waxes are mainly composed of fatty acids combined with monohydric alcohols possessing a high molecular weight. For instance, spermaceti contains the palmitic ester of cetyl-alcohol,

and beeswax the palmitic ester of myricyl alcohol. Paraffin wax is a hydrocarbon and not a true wax.

Cetaceum (spermaceti) is a fatty body which crystallises from sperm oil. It consists almost entirely of cetyl-palmitate, $C_{15}H_{31}.COOC_{16}H_{33}$, with small quantities of allied esters.

Cera alba (white beeswax).—The wax from the honeycomb of the hive-bee bleached by air and sunlight.

Cera flava (yellow beeswax) is a secretion of the hive-bee and constitutes the walls of the honeycomb. Beeswax contains over 80 per cent. myricyl palmitate, $C_{15}H_{31}COOC_{30}H_{61}$, about 15 per cent. cerotic acid, $C_{26}H_{53}COOH$, and an aromatic body, cerolein.

Petroleum

Petroleum, or rock oil, is found in certain geological strata, and results from the decomposition of organic matter. When petroleum is subjected to fractional distillation four main fractions are obtained:—(1) The mineral naphtha distils over. (2) "Burning" oils. (3) Lubricating oils. (4) A soft paraffin is left in the still which, when purified, becomes vaselin.

These bodies are pharmacologically allied to fats, though chemically, of course, they are quite distinct.

Paraffinum durum is a mixture of the higher members of the paraffin series. It consists of hydrocarbons ranging from $C_{20}H_{42}$ to $C_{30}H_{62}$. The melting-point required by the Pharmacopœia should be between 54.4 and 57.2° C.

Paraffinum liquidum is an oily liquid obtained by fractional distillation from petroleum. It is a popular aperient.

Paraffinum molle (vaselin) is a semi-solid mixture of various hydrocarbons, $C_{15}H_{32}$ to $C_{20}H_{42}$, remaining in the still after petroleum distillation.

Benzol contains about 70 per cent. benzene, C_6H_6, and the rest toluene, $C_6H_5CH_3$, and some xylene, $C_6H_4.CH_3.CH_3$. It is used as a solvent for india-rubber. One application will often destroy pediculi capitis and pediculi pubis. It has no chemical relationship with the paraffins.

Soaps

Saponification, in its widest sense, now indicates the decomposition of an ester into alcohol and acid, although it had its origin in the decomposition of oils by caustic alkali in making soap.

$$\underset{\text{Olein.}}{C_3H_5(C_{18}H_{33}O_2)} + 3NaHO = \underset{\substack{\text{Sodium oleate}\\ \text{(hard soap).}}}{3NaC_{18}H_{33}O_2} + \underset{\text{Glycerin.}}{C_3H_5(OH)_3}$$

Sapo animalis (curd soap) is prepared from a purified animal fat, and is composed mainly of sodium stearate.

Sapo durus (hard soap) is prepared from olive oil, and is, therefore, composed almost entirely of sodium oleate.

Sapo mollis is prepared from olive oil by using caustic potash instead of soda.

Glycerin, $C_3H_5(OH)_3$, may be conveniently considered here. It is an alcohol obtained during the preparation of soap and stearin candles. Glycerin is very useful in pharmacy on account of its solvent action. Its boiling-point is so high that it is hardly volatile at ordinary temperatures, and being hygroscopic it even absorbs water from the air and increases in volume.

Action.—The emollients are chemically indifferent substances, and, on account of their insolubility, exert no "salt action." They are employed for several purposes. First, as protectives to the skin: by their means the irritation of a diseased surface may be allayed either by preventing the part from drying or by protecting it from dust, bacteria, or irritating gases. Secondly, they soften the skin and render it more elastic; this would seem to be produced by the penetration of the fat into the stratum corneum, and possibly also by the rubbing: in this way they relieve the tension and pain in inflamed parts. Thirdly, they are sometimes employed to promote the absorption of drugs. The stratum corneum is not permeable to water or other liquids, and so absorption can only take place through the glandular structures of the skin, and these are filled up with fatty material. This sebum effectually prevents the penetration of water, but not of fats; so it is possible, by making an emulsion of a drug with a fatty basis, aided by suitable rubbing, to promote the absorption of the drug. Alcohol also dissolves away the sebum, and substances dissolved in it may also be absorbed. Fatty substances form the basis of ointments.

Olive oil is administered internally in ounce doses: it produces soft stools, and at the same time protects the bowel from irritation. Linseed oil is also laxative: as an emulsion with lime water (carron oil) it forms a favourite application to burns.

Hard paraffin has been recently successfully employed as a hypodermic or submucous injection to remedy facial deformities.

Soaps are employed as excipients for pill masses and as vehicles for liniments and plasters. They are also mild laxatives, and assist in the emulsification of fat in the small intestine. When introduced into the rectum as an enema they facilitate the softening of hard scybalous masses, and by their irritating properties induce reflex contraction of the rectum, and sometimes of the entire colon.

Glycerin, although not a fat, resembles these substances very closely. It is somewhat irritant to the unbroken skin, and the irritation may be severe if the glycerin is applied to the conjunctiva: the irritant effect is due to the abstraction of fluid from the tissues. The drug is used as a protective to slight wounds, fissures and cracks in the lips. When small quantities are injected into the rectum it causes an augmented peristalsis and evacuation of the bowels. The effect is reflex, and induced by the local irritation in the lower part of the rectum.

Glycerin has some value as an antiseptic, probably acting by osmosis.

Taken internally it is a demulcent. It is readily absorbed, and undergoes oxidation in the tissues, so that it must be regarded as nutrient, but to substitute it for cod-liver oil as a food, as has been done, is a proceeding wholly unwarranted by the evidence.

In large doses mental symptoms accrue, such as restlessness and tremors; and the latter may culminate in tetanic convulsions. Death occurs from respiratory failure. The urine not infrequently contains hæmoglobin; this condition only obtains when the drug is taken by the mouth, or, better, injected subcutaneously, and is not observed when the glycerin is injected intravenously. No satisfactory explanation of this fact is forthcoming.

It is especially useful in the application of remedies to the skin since it does not evaporate but takes water from the air; the drug thus remains in solution and active.

DEMULCENTS

Acaciæ gummi (gum arabic) is a dried exudation from the branches of various species of acacia. It consists chiefly of arabic acid combined with calcium, magnesium, and potassium. On boiling with dilute acids the arabic acid is converted into pentose. Gum acacia also contains a diastatic ferment, and its solutions are apt to form irritating compounds; hence, in medicine only the freshly prepared mucilage should be used.

Tragacantha.—Tragacanth is the exudation from *Astragalus gummifer*. It contains 60 to 70 per cent. traganthin, which is an insoluble compound of arabic acid. With water it swells up to a jelly.

Lini semina (linseed), from the flax *Linum usitatissimum*. The epithelium contains 15 per cent. mucilage, which is derived from starch, and 30 to 40 per cent. of fixed oil. Lini Semina contusa, or crushed linseed, is also official.

Amylum ($C_6H_{10}O_5$) is procured from the grains of wheat.

Glycyrrhiza (liquorice root from *G. glabra*).—It contains 7 per cent. glycyrrhizin, a sweet principle, together with proteid, sugar, resin, and asparagin.

Amygdala dulcis (sweet almonds), seeds of *Prunus amygdalus*. They contain 45 per cent. fixed oil and about 20 per cent. proteid, and an enzyme, emulsin.

Gelatinum is an albuminoid substance, from bones, ligaments, and other animal tissues. When taken internally it acts as a circulating, but not a tissue, protein. It is sometimes injected to stop hæmorrhage: the beneficial results are believed to be due to its high calcium content, which is about 6 per cent.

Gossypium (cotton-wool) is the hairs of the seeds of species of gossypium. It is chiefly cellulose with traces of albuminoids and salts.

Pyroxylinum (di-nitrocellulose) is prepared by the action of nitric acid on cotton-wool.

$$\underset{\text{Cellulose.}}{C_6H_{10}O_5} + 2HNO_3 = \underset{\text{Di-nitrocellulose.}}{C_6H_8(ONO_2)_2O_3} + 2H_2O$$

It would be more correct to speak of this body as cellulose nitrate.

Collodion is a solution of pyroxylin in a mixture of ether and alcohol.

Acetonum, $CO(CH_3)_2$, has an action very similar to that of ethyl alcohol. It is a useful solvent of resins, fats, cantharidin, pyroxylin, and celluloid.

Carbon bisulphide (CS_2) is used as a solvent for india-rubber and phosphorus.

Action.—The demulcents are drugs which exert a soothing action on mucous membranes. This they do by mechanical means, simply covering over the affected surface and preventing irritation from secretions or foreign matter. Thus, they are useful as a basis for cough mixtures and in the after treatment of irritant poisoning, acting by producing a thin coating over the pharyngeal and gastro-intestinal membranes respectively. Demulcents affect the sensation of taste. Sugar in water alone is sweeter than if mucilage is present, and mucilage masks acid even more than sweet tastes. Demulcents also affect temperature sensation; cold water tastes colder than milk at the same temperature. The same is true of other sensations. If a decerebrate frog hanging by a thread from its jaw has a hind foot placed in 0·1 per cent. hydrochloric acid, the limb is withdrawn in a few seconds: the presence of gum in the acid delays the reflex often for some minutes. In the alimentary canal not only do they prevent irritation by coating the mucous membrane and enveloping irritant particles, but they delay absorption. We have already noted the advantage of administering certain drugs, the absorption of which is not required, in their crude form with the natural gums, resins, and other colloids; aloes and kino will serve as examples.

Gum acacia is feebly nutritive, and is partly converted into sugar in the small intestine. It is largely employed for making emulsions and for suspending insoluble powders. Tragacanth is only used for suspending heavy metallic powders in mixtures. Linseed, besides its demulcent action, has a diuretic effect.

Starch is a valuable foodstuff: it is employed as a dusting powder for protecting surfaces. Liquorice, on account of its pleasant sweet taste, is a favourite demulcent in cough mixtures; it is also slightly laxative. Gelatin is official in order to obtain a basis for gelatin suppositories. When it is directly applied to bleeding surfaces it acts as a powerful hæmostatic. Its injection as a hæmostatic for internal hæmorrhage is of very doubtful value. It has been employed in hæmaturia, purpura, and to promote the formation of clot in aneurysms.

Collodium is only employed externally. When the ethereal solution is placed on the skin the ether almost immediately evaporates, leaving a thin film impervious to moisture. This contracts, puckers up the surrounding skin, and partly empties the vessels. It is a useful protective coating for fresh wounds. Cotton-wool and india-rubber are employed entirely as protectives to the skin.

Carbon bisulphide (4 m. to a pint of water) is an excellent antiseptic. Its inhalation produces anæsthesia like chloroform. It is introduced into the Pharmacopœia as a solvent.

SUGARS

Saccharum purificatum ($C_{12}H_{22}O_{11}$), supposed to be prepared from the juice of the sugar-cane, but much is also secured from sugar-beet. It is hydrolysed by dilute acids to glucose.

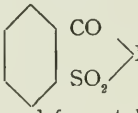
$$C_{12}H_{22}O_{11} + H_2O = 2C_6H_{12}O_6$$

Saccharum lactis (milk-sugar or lactose, $C_{12}H_{22}O_{11}.H_2O$, isomeric with cane-sugar) is prepared from milk-whey, and is present in cow's milk to about 5 per cent. It does not absorb water or become lumpy like cane-sugar, and is suitable for the dilution of potent drugs. It is hydrolysed by treatment with acids.

Syrups are solutions nearly saturated with refined cane-sugar. They are used to flavour, as preservatives, and to retard chemical changes. Simple syrup is composed of a solution of 2 parts sugar and 1 part water.

Glucosum ($C6H_{12}O_6$) is obtained by the invertion of starch. It is soluble in water, alcohol, or glycerin. It is used as a food and for pharmaceutical purposes.

Mel depuratum (clarified honey) is the secretion from the honeycomb of Apis mellifica. It is composed of from 70 to 80 per cent. glucose, some dextrin, wax, proteid, volatile oil, and a minute quantity of formic acid which acts as a preservative.

Glusidum (saccharin),  , is an imide having a very sweet taste, and is prepared from toluene. When absolutely pure its sweetening power is said to be from 500 to 600 times stronger than sugar. It is excreted unchanged in the urine.

Action.—The sugars are valuable foodstuffs. They are employed in medicine mainly for flavouring and preservative purposes: dilute solutions of sugar ferment easily, but saturated solutions may be preserved indefinitely on account of the osmotic conditions preventing growth of lower organisms (salt action).

Solutions of sugar possess the property of dissolving much $Ca(OH)_2$ to form calcium saccharate, and they also retard the oxidation of ferrous salts, hence their use in the preparation of Ferrum carbonas saccharatus.

Milk-sugar is diuretic; it is less liable to fermentation than cane-sugar, and is therefore employed to sweeten the food of the dyspeptic. Honey is employed only as a vehicle for active remedies. Lævulose was at one time prescribed for diabetics on the supposition that they were able to assimilate this sugar. Unfortunately this is not the case, and diabetics excrete it in the urine as glucose.

Most coal-tar derivatives, if administered continuously and for some time, produce irritation of the kidneys and albuminuria. It is not yet certain whether saccharin has this effect.

COLOURING AGENTS

Coccus (cochineal) is the dried fecundated female insect *Coccus cacti*. It contains about 10 per cent. of a colouring matter, carminic acid, 10 per cent. myristin, with fats and wax. Carmine is prepared by precipitating a decoction with alum, and consists of 50 per cent. carminic acid.

Pterocarpi lignum (red sandal-wood) is the heart-wood of *Pterocarpus santalinus*. The colouring matter, santalin, is a resinous substance precipitated from alkaline solutions by the addition of acid.

Rhœados petala (red poppy petals).—They contain 0.2 to 0.5 per cent. morphine. The colouring matter has not been isolated.

Action.—All these bodies are employed for colouring purposes only. Pterocarpus has very slight astringent properties on account of a trace of tannic acid. Rhœados has a very feeble—quite insignificant—narcotic effect.

MATERIA MEDICA

Oils and Fats :—

Adeps.
Adeps Benzoatus.
Adeps Lanæ.
Adeps Lanæ Hydrosus.

PREPARATION

Unguentum Lanæ Compositum.

Sevum Præparatum.

Acidum Oleicum.—Lead plaster contains oleate of lead. Oleate of zinc is used in an official ointment. The oleate of mercury is official.

Oleum Olivæ. Dose, ½ to 1 oz.
Oleum Amygdalæ.
Oleum Lini.
Oleum Theobromatis.
Oleum Ricini and Oleum Crotonis.—Purgatives.

Waxes :—

Cetaceum.

PREPARATION

Unguentum Cetacei.—Spermaceti, white beeswax, liquid paraffin.

Cera Alba.
Cera Flava.
Paraffinum Liquidum.
Paraffinum Durum.
Paraffinum Molle.

PREPARATION

Unguentum Paraffini.—Hard paraffin, soft paraffin, beeswax.

Benzol.

Soaps :—

Sapo. Animalis.
Sapo. Durus.

PREPARATIONS

1. Emplastrum Saponis.—Hard soap and lead plaster
2. Pilula Saponis Composita.—Containing opium.
   Dose, 2 to 4 grs.

Sapo. Mollis.

PREPARATION

Linimentum Saponis.—Opodeldoc. Contains camphor

Glycerinum.

PREPARATIONS

1. Glycerinum Acidi Borici.—30 per cent. solution.
2. Glycerinum Acidi Carbolici.—1 in 6.
3. Glycerinum Acidi Tannici.—1 in 6.
4. Glycerinum Aluminis.
5. Glycerinum Amyli.
6. Glycerinum Boracis.
7. Glycerinum Pepsini.—1 dr. represents 5 grs. of pepsin.
   Dose, 1 to 2 drs. (4 to 8 mils).
8. Glycerinum Plumbi Subacetatis.
9. Glycerinum Tragacanthæ.
10. Suppositoria Glycerini.

Demulcents :—

Acaciæ Gummi.

PREPARATION

Mucilago Acaciæ.

Tragacantha.

PREPARATIONS

1. Glycerinum Tragacanthæ.
2. Mucilago Tragacanthæ.
3. Pulvis Tragacanthæ Compositus.
   Dose, 20 to 60 grs. (6 to 40 degrms.).

Lini Semina and Lini Contusa Semina.

Amylum.

PREPARATION

Glycerinum Amyli.

Glycyrrhizæ Radix.

PREPARATIONS

1. Extractum Glycyrrhizæ.—Chiefly used as an excipient.
2. Extractum Glycyrrhizæ Liquidum.
   Dose, ½ to 1 dr. (2 to 4 mils).
3. Pulvis Glycyrrhizæ Compositus.—Senna, liquorice root, sublimed sulphur.
   Dose, 60 to 120 grs. (4 to 8 grms.).

Amygdala Dulcis.

PREPARATIONS

1. Pulvis Amygdalæ Compositus.
2. Mistura Amygdalæ.
   Dose, ½ to 1 oz. (15 to 30 mils) used as a vehicle.

Gelatinum.

Gossypium.

Pyroxylinum.

PREPARATIONS

1. **Collodium.**—Pyroxylin, dissolved in ether and alcohol.
2. **Collodium Flexile.**—Collodium, 48 ; Canada balsam, 2 ; castor oil, 1. Protective like collodium, but less liable to crack.
3. **Collodium Vesicans.**—Pyroxylin, 1 ; dissolved in Liquor Epispasticus, 40.

Carbon Bisulphidum.

Sugars :—

Saccharum Purificatum.

PREPARATIONS

1. **Syrupus.**
2. **Syrupus Glucosi.**

Glucosum.

Saccharum Lactis.

Mel Depuratum.

PREPARATION

Oxymel.—Honey with a little acetic acid.
Dose, 1 to 2 drs. (4 to 8 mils).

Glucidum.—Saccharin.

Colouring Agents :—

Coccus.

PREPARATION

Tinctura Cocci.
Dose, 5 to 15 m. (3 to 10 decimils).

Pterocarpi Lignum.

Rhœados Petala.

PREPARATION

Syrupus Rhœados.
Dose, ½ to 1 dr. (2 to 4 mils).

CHAPTER XXXII

FERMENTS. COD-LIVER OIL. VEGETABLE TOXINS. INTERNAL SECRETIONS. SERUM THERAPY. ANTAGONISM

FERMENTS

Pepsin is an enzyme obtained from the mucous membrane of the pig's, sheep's, or calf's stomach. It possesses the power, in the presence of warmth, acidity, and moisture, of hydrolysing proteids into peptones. It digests only in acid solution, and its optimum action occurs when the percentage of hydrochloric acid is between 0.2 and 0.4 per cent. A deficiency of gastric juice is known to occur in the aged who suffer from chronic wasting diseases, especially cancer; and so pepsin and hydrochloric acid are rationally indicated in such conditions. Nutrient enemata and suppositories require to be pre-digested, the rectum being poorly provided with ferments. Pepsin is sometimes used to pre-digest albuminous food, although pancreatic extract is on the whole more valuable for this purpose.

Liquor pancreatis is an extract of the fresh pancreas from the pig. It contains at least four ferments, the most important being trypsin, which converts proteids into peptones. Another ferment coagulates milk, a third emulsifies fats, and a fourth hydrolyses starch into sugar. If the extract is prepared very carefully, so that it in no way becomes contaminated with intestinal secretion, it is inactive. The extract contains zymogens, but no enzymes. The conversion of the trypsinogen into trypsin is affected by another enzyme, enterokinase, which occurs in abundance in the mucous membrane of the duodenum. Pancreatic ferments require an alkaline medium, and their activity is destroyed by the hydrochloric acid in the stomach. To be of value, they must produce their effect before the acid juice is secreted: the best result is seen in the case of infants who have been deprived of their normal food. Many of the artificial foods are composed of ordinary flour which has been partly converted into dextrine by dry heat: Benger's Food is such a substance, with the addition of pancreatic extract. The principal use of these extracts is that of digesting foods before they are taken internally. They are therefore employed for peptonising milk and farinaceous foods, and may, with sodium carbonate, be advantageously added to nutrient enemata.

MATERIA MEDICA

Pepsinum. **Dose, 5 to 10 grs.** (3 to 6 dcgrms.).

PREPARATION

Glycerinum Pepsini.—1 dr. represents 5 grs. of pepsin.
Dose, 1 to 2 drs. (4 to 8 mils).

Liquor Pancreatis. **Dose, 1 to 2 drs.** (4 to 8 mils).

Certain vegetable ferments are also employed in medicine: three of these only require mention.

Malt extract, besides containing foodstuffs, has a digestive ferment, diastase, which converts starch into maltose. Malt is barley which has been allowed to germinate a few days, thus converting a considerable amount of its starch into sugar, and then heated to a certain temperature. If this temperature is too high the diastase is destroyed, and this is the reason so many of the extracts on the market are inert. The value of malt taken internally depends rather on its high nutritive power than upon the diastase it contains.

Taka-diastase is a ferment prepared from the fungus Eurotium. It is extremely active, much more so than ordinary diastase, and converts in a few minutes a hundred times its weight of starch into maltose. It ceases to act in acid solution of a greater strength than 0.1 per cent., and is, therefore, prescribed internally along with sodium carbonate.

Papain is another ferment obtained from the juice of *Carica papaya*. It acts either in moderately acid or alkaline solutions and at the body temperature; it is, therefore, taken internally in cases of dyspepsia, since its power of peptonising albumens continues all down the intestines. Papain has been used for application to diphtheritic membranes, which it digests. It has also been injected into tumours with the object of effecting their absorption; and peptones have been found as a result of their partial digestion.

COD-LIVER OIL

Cod-liver oil is extracted from the cod's liver. Formerly this was done by leaving the livers to decompose and collecting the oil which was thus set free. Now a steam process is employed and the oil is melted out from the fresh livers, in some cases without contact with the air. There is reason to believe that some of the oil on the market comes from other fish, such as shark's liver.

The composition of cod-liver oil is stated to be different from that of other oils. Instead of containing palmitin, stearin, and olein, it is believed to contain only about 4 per cent. of palmitin, and none of the other two. In their place therapin and jecolein

are found, which are glycerides of unsaturated acids. These tend to form oxyacids in the air. The oil contains from ½ to 5 per cent. of free acid, traces of iodine, bromine, phosphorus in organic combination, and cholesterin. It also contains several amines, such as butyl-amine ($C_4H_9.NH_2$) and amyl-amine ($C_5H_{11}.NH_2$). Formerly the oil was dark in colour and extremely objectionable to the palate: it contained 6 or 7 per cent. of acid and a considerable quantity of leucomaines. The modern oil is almost tasteless, possesses little more than ½ per cent. acid and a very small quantity of leucomaines. If it is exposed to the air it easily oxidises and becomes rancid, and one method which has been adopted as a preservative is to keep it saturated with carbonic acid.

Cod-liver oil must be regarded as a food and not a drug: it is the most easily assimilable of all fats. It increases weight and improves the condition of the patient generally: many people who are unable to digest ordinary fats can often digest this oil. In the case of infants suffering from wasting disease the oil is advantageously administered by rubbing it into the skin. Its value as a food is beyond dispute. Two reasons have been given for this:—(1) This fat has a different composition from other fats and is more rapidly oxidised. (2) The fat is stated to be more readily absorbed. From experimental evidence, it is extremely probable that one function of the liver is the preparation of fatty acids of a high degree of unsaturation for the further processes of metabolism, and, if this is so, it might well be expected that cod-liver oil would have some action on metabolism different from that of other fats. Williams has shown that the administration of this oil increases not only the total absorption of fat, as of course it should, but also the percentage absorption of all fats taken, and further, that it influences the retention of nitrogen favourably. Cod-liver oil is clearly, then, a different kind of food from other fats, such as cream and butter, and when general metabolism is abnormal it may supply a deficiency.

Besides this action, it has been shown also that cod-liver oil *in vitro* dissolves the fatty envelope which surrounds the tubercle bacilli, and retards the growth of the organism.

MATERIA MEDICA

Oleum Morrhuæ. Dose, 1 to 4 drs. (4 to 16 mils).

CHAULMOOGRA OIL

Chaulmoogra oil is a fixed oil, like cod-liver oil, composed of unsaturated fatty acids. It is expressed from the seeds of *Taraktogenos kurzii*, and is usually seen as a soft fat. It has been used as a counter-irritant, but its principal use is in leprosy, in the treatment of which disease it has given better results than any other remedy.

It is used freely both internally and externally, generally as the sodium salt. How it acts we do not know, but it is stated to stimulate the leucocytes to greater activity, and like cod-liver oil to penetrate the wall of the leprosy bacillus, rendering it more vulnerable. Dose, 10 m. to 60 m.

VEGETABLE TOXINS

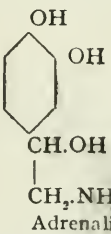
There are certain bodies occurring in the vegetable kingdom which bear a close resemblance, both in constitution and action, to the animal toxins. Ricin is one such body contained in castor-oil seeds. It is a powerful poison, $\frac{1}{10000}$ mg. per kilo body-weight being fatal to rabbits. A small injection of this substance gives rise to acute gastro-enteritis, with intestinal hæmorrhages, swelling of the lymphatic glands, and ecchymoses throughout the great omentum. Death in these cases occurs several days after the injection. If ricin is given by the mouth it exerts little or no irritant action, and the drug is rendered harmless in the stomach. It does not exist in castor oil.

As examples of other allied vegetable toxins, abrin from jequirity seeds and crotin from croton seeds may be mentioned.

ANIMAL EXTRACTS

Adrenalinum

Adrenalin is the name given to the active principle of the suprarenal glands. It has the composition shown below. It forms salts of which the chloride is freely soluble in water, and solutions kept out of contact with the air and in the presence of some antiseptic can be preserved indefinitely. This drug has a most remarkable action; its effect upon any structure is invariably that which follows excitation of the sympathetic nerves supplying the tissue.



Adrenalin.

Natural adrenalin is lævo-rotatory; synthetical adrenalin is optically inactive and has only about half the toxicity of the natural variety, because it is a mixture of two stereoisomers, the *d* variety being inactive (*cf.* Hyoscyamine).

Adrenalin is also present in many invertebrate animals, and is present in considerable quantities in the poison glands of *Bufo agua*, an American toad.

The following effects are only obtained when the drug is injected into the blood.

Circulatory System.—Adrenalin enormously accelerates and augments the force of the beat of the isolated mammalian heart

(Fig. 87). This action is much greater than can be obtained with any other drug, but its duration is very limited.

Perfusion of the drug through an isolated organ the vessels of which are innervated by the sympathetic gives rise to an intense constriction, so that outflow from the vein almost ceases. Perfusion through vessels which are not much innervated, as those of the lungs, liver, brain, and heart, has no marked effect. If adrenalin is administered to the intact animal, it therefore causes a great rise in blood-pressure: the heart-beat is at first retarded reflexly by this big pressure, but if the vagi be cut it becomes decidedly quicker (Fig. 88).

The Alimentary Tract.—Adrenalin inhibits the movements of the stomach and intestines in mammalia except the ileo-colic sphincter, which contracts. Other plain muscle, such as that of the spleen, is also powerfully excited (Fig. 89). The *lungs*, which develop as outgrowths from the alimentary canal, are also affected by adrenalin, and the bronchioles are made actively to dilate, so that adrenalin is usefully employed in the treatment of spasmodic asthma (Fig. 90).

Genito-urinary Tract.—There is pronounced contraction of the ureter, vas deferens, and seminal vesicles. The bladder, on the contrary, is inhibited. The muscles of the hair contract, and the hairs in consequence become erected.

In many animals adrenalin contracts the pregnant uterus and relaxes the non-pregnant. The uterus is supplied by both inhibitory and augmentor sympathetic fibres, and the action of adrenalin should be regarded as the mean of two effects: during pregnancy the augmentor fibres increase greatly with the growth of the uterine muscle, and adrenalin increases tone and peristalsis.

The Eye.—Adrenalin causes dilatation of the pupil, withdrawal of the nictitating membrane, separation of the eyelids, and protrusion of the eyeball; this effect is seen best in the cat.

There is a small secretion of thick viscid saliva.

We believe that these effects are entirely on the so-called sympathetic "nerve-endings," and the reasons for this statement are as follows:—

(1) The effect always corresponds exactly with that of sympathetic excitation.

(2) Perfusion through vessels which have little sympathetic supply, such as the pulmonary or cerebral, produces little effect, yet these vessels contract to muscle-poisons, such as barium or veratrine, quite typically.

(3) If the vaso-motor "nerve-endings" in any vessels are paralysed with apocodeine, adrenalin no longer produces constriction, although the muscle is still intact, as shown by its response to barium.

The introduction of adrenalin into the circulation at all times produces a very fugitive effect, and the adrenalin is destroyed. This destruction apparently goes on at the "nerve-endings" until

these are saturated; for we know that after perfusing the drug through innervated vessels only a certain amount is destroyed. What apparently happens is a combination between the adrenalin and some constituent at the periphery, which results in stimulation of the muscle, and when all this latter substance is used up, the adrenalin circulates free in the blood and produces no further effect.

The application of this drug to disease results in different effects, according to the mode of its administration.

Locally applied to mucous membranes, it causes intense constriction of the peripheral vessels, and so arrests bleeding. It may be taken internally for bleeding from the stomach (hæmatemesis), but it is valueless in cases of remote hæmorrhage, because the drug is destroyed before or during absorption. Adrenalin is also valuable in post-partum hæmorrhage in the form of an injection, and acts by constricting both the vessels and the uterine muscle.

Subcutaneous injections give rise to local constriction of the vessels, but when the dose is moderate ($\frac{1}{100}$ gr.) there is no general systemic effect. It is often given along with local anæsthetics, such as cocaine, novocaine, and stovaine, as by constricting vessels it will retard general absorption. It is also useful in the treatment of spasmodic asthma.

In man and animals subcutaneous intraperitoneal and intravenous injections of adrenalin cause glycosuria even when all the glycogen has been removed from the liver by fasting and the diet contains no carbohydrate. The explanation of this is not clear, but the amount of sugar excreted is said to be proportional to the amount of adrenalin reaching the circulation. By using this method and comparing the amount of sugar excreted by intravenous and subcutaneous injections, it may be inferred that 94 per cent. of the latter fails to reach the circulation.

Intravenous injection gives rise to all the effects we have already noted. It may be valuable in cases of sudden cardiac failure, for as soon as the drug reaches the heart it enormously increases both the force and frequency of its beat.

It is quite clear, then, that adrenalin cannot act on the nerve-endings in the ordinary sense, that is, the terminal fibres as revealed by methylene blue, since tissues in which all the sympathetic nerves have been cut and allowed to degenerate still respond to adrenalin and are sometimes supersensitive to it.

Adrenalin certainly does not act on the contractile substance. The proofs in this case seem overwhelming. First, as already pointed out, we can antagonise the effects of adrenalin, either the motor only (ergotoxin) or the whole effect (apocodeine), leaving the response of the muscle to mechanical or chemical stimuli intact. Secondly, the established fact that the response of plain muscle to adrenalin is determined by the presence of a sympathetic nerve-supply.

To meet these requirements the term myo-neural junction has been employed, a tissue not necessarily being an integral part of either the nerve or muscle; or we may simply refer to the seat of action as on the β, a position on which atropine and pilocarpine also act, though on different parts of the tissue.

MATERIA MEDICA

Adrenalinum.—The lævo variety only is official.

Liquor Adrenalini Hydrochloricus. Dose, 10 to 30 m. (6 to 8 decimils). **0.1 per cent.**

Secretin

When hydrochloric acid reaches the duodenum from the stomach, it combines with or renders soluble some body present in the epithelial cells of the duodenum, called prosecretin: the resultant soluble substance has been termed secretin by Bayliss and Starling. This body has a specific action on the pancreas, and produces a big flow of juice. In this process the secretin is destroyed, and appears to enter into chemical combination with some constituent of the pancreas. We are inclined to think that one of these bodies is a protrypsinogen, and that the combination of secretin and protrypsinogen gives rise to trypsinogen, which is excreted, and on reaching the intestine is converted by a ferment enterokinase into trypsin. The destruction of the secretin, whilst inducing glandular activity, is analogous to the destruction of adrenalin during sympathetic activity.

If secretin is injected subcutaneously when no food is passing through the duodenum, the flow of pancreatic juice may cause inflammation of the mucous membrane of the duodenum. The prolonged use of secretin leads to great tissue-breakdown and an excessive excretion of nitrogen, sulphates, phosphates, and chlorides in the urine. But sugar or albumen is not present.

The clinical indications for the employment of secretin are at present undefined.

Starling has recently proposed the generic name *hormone* for the chemical bodies occurring naturally in the animal body which specifically excite tissues. Two are known which excite glands, secretin and a second substance which is obtained by boiling a watery extract of fœtus. If such a solution is injected at intervals into a female animal, the mammary glands begin to develop even in the virgin, and the development proceeds to the milk-secreting stage.

Thyroid Gland

In 1856 Schiff showed that thyroidectomy was fatal to animals. In 1882 Kocher and Reverdin compared the condition of a patient whose thyroids had been removed with the disease myxœdema. It

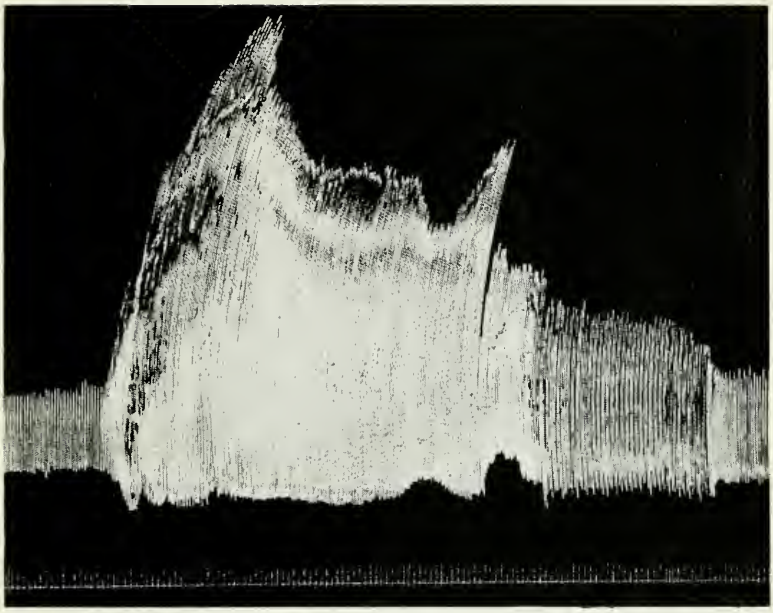


FIG. 87.—RECORD OF THE MOVEMENTS OF AN ISOLATED RABBIT'S HEART DURING PERFUSION WITH RINGER'S SOLUTION.

Shows the effect of introducing adrenalin (1 in 100,000) into the circulating fluid for a period of thirty seconds. Note the great acceleration and increased force of beat. Time = secs.

To face p. 442.

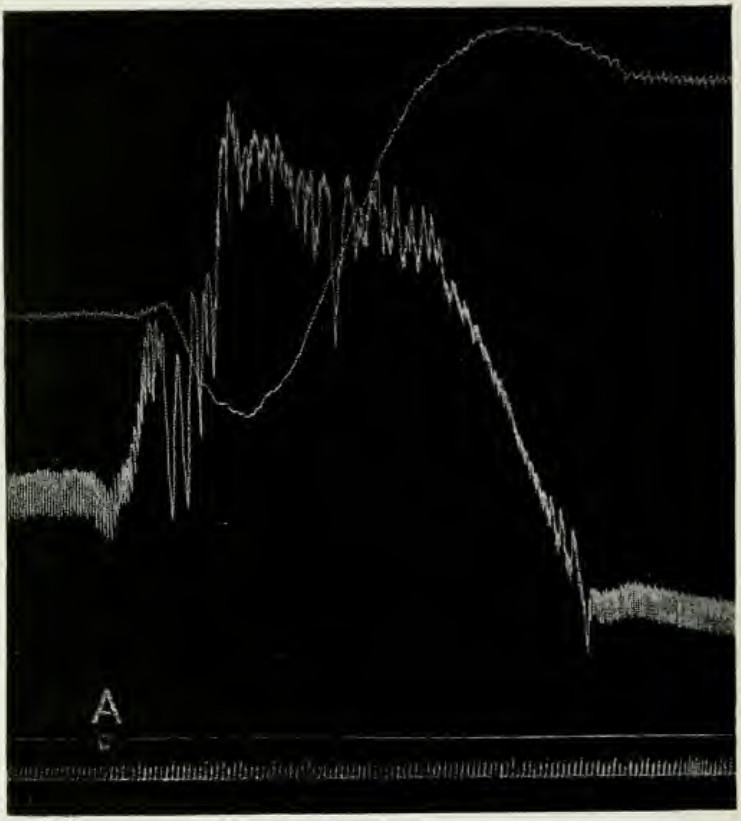


FIG. 88.—CAT. INTESTINAL VOLUME AND BLOOD-PRESSURE.

At A 1 c.c. of a solution of 1 in 50,000 adrenalin was administered by the jugular vein. The blood-pressure rises partly from increased cardiac output and partly, as shown in this figure, from vaso-constriction. As the vessels begin to dilate blood-pressure falls to a point below the normal. Note the cardiac inhibition during the rise in pressure. This is due to stimulation of the medulla by the increased pressure and so does not occur if the vagi are severed. Time = secs.

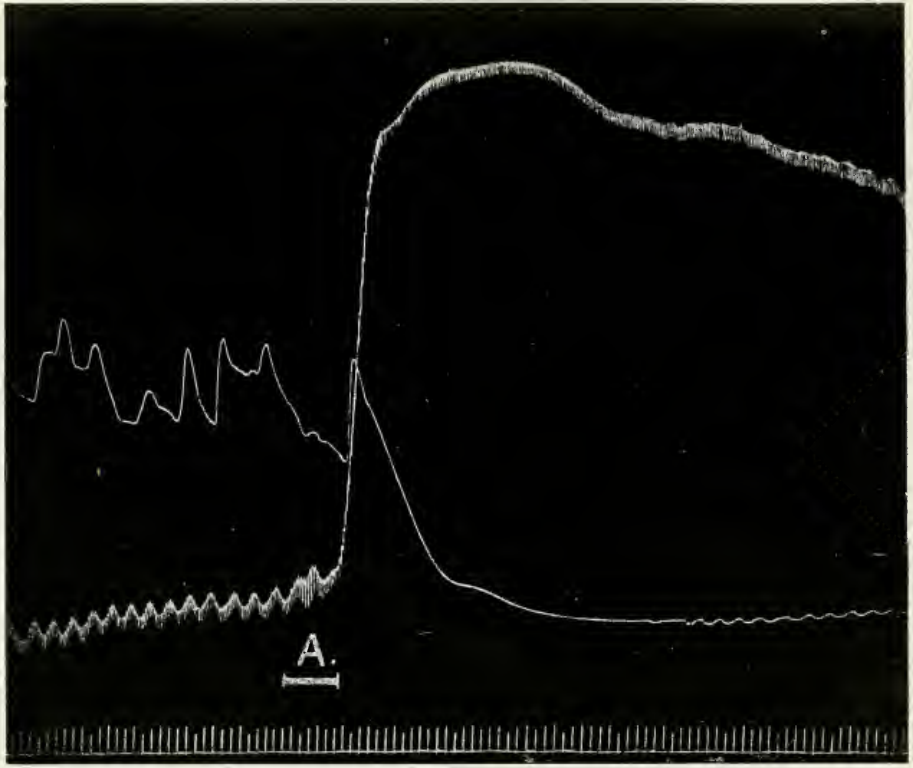


FIG. 89.—CAT. INTESTINAL MOVEMENTS AND BLOOD-PRESSURE.

The intestine is made to record by fixing a balloon in its lumen. The balloon is filled with air and communicates with a manometer, so that the height of the fluid in the manometer records the degree of contraction or relaxation of the intestine. At A 1 c.c. of a 1 in 20,000 adrenalin chloride was injected into a vein. The intestinal movements are at once inhibited and the blood-pressure rises. Both these effects correspond to excitation of sympathetic nerves.
Time = secs.

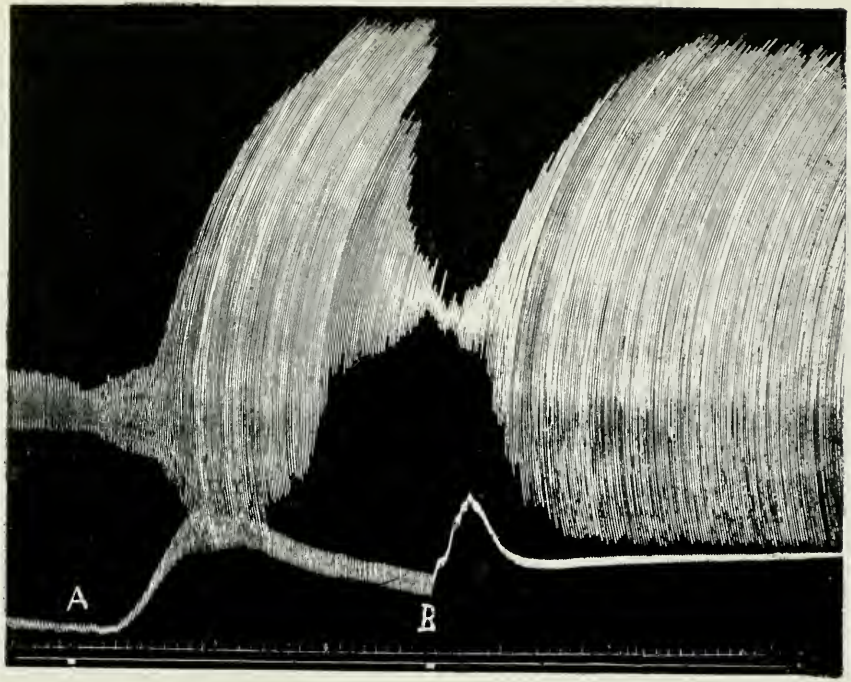


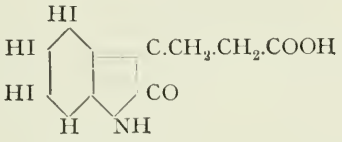
FIG. 90.—RECORD OF A LUNG VOLUME—THAT IS, THE AMOUNT OF AIR PASSING IN AND OUT OF ONE LOBE OF THE LUNG—AND THE BLOOD-PRESSURE OF A CAT.

At A adrenalin was given intravenously: note the wide broncho-dilatation and the rise of blood-pressure; both effects are due to sympathetic stimulation. At B atropine was given: note the permanent broncho-dilatation and the rise in blood pressure from cardiac acceleration; both effects are due to vagal paralysis. Time = 5 secs.

To face p. 443.

soon became evident that this disease was brought about by a deficiency of thyroid secretion, and could be cured by grafting the gland under the skin, by injecting an extract of the gland subcutaneously, or by eating the gland.

The active principle of the gland occurs in the colloid material, and, as it is not destroyed by concentrated acids nor by peptic digestion, it is readily separated from protein material. This substance has been termed thyroxin; it is an oxyindole derivative containing iodine in the benzene nucleus and is related to tryptophane:



Thyroxin.

Thyroidectomy.—If the thyroid gland is removed from dogs, they rapidly exhibit increased reflex excitability, and occasionally show intermittent convulsions. Death occurs in a few days. If a dose of thyroid is injected into a vein a few hours before death all the vital functions are stimulated; the heart, for example, beats more vigorously, and the blood-pressure rises.

The symptoms in man and monkey after thyroidectomy are produced much more slowly, and are characterised by a peculiar growth of connective tissue, which is very rich in mucus and particularly prevalent in the skin. This condition is also characteristic of myxœdema. In the rabbit, thyroidectomy does not produce death, but if the parathyroids are also removed death ensues very rapidly.

The continued administration of thyroids to healthy individuals results in profound changes in the nervous and circulatory systems and on metabolism.

Metabolism is greatly increased; the excretion of nitrogen, sulphur, and phosphorus in the urine is augmented. The gaseous exchange is also greater, and the weight of the patient falls. There is a great rise in the amount of oxygen taken in, and a very considerable but relatively smaller increase in the carbonic acid elimination. The loss of weight is much greater than can be accounted for by destruction of protein tissue, and we are led to the conclusion that there is an augmented consumption of fat.

It is well known that if we increase the amounts of carbohydrates and fat in the fixed diet of a man who is in nitrogenous equilibrium, we diminish the amount of protein-breakdown in the body, that is, carbohydrates and fats are protein-sparers. Thyroid feeding gives rise to an excessive tissue-waste, which is not stayed by the administration of carbohydrate or fat. But this augmented

protein-breakdown only accounts for about one-sixth of the loss of weight; the rest must, therefore, be due to the oxidation of fat and to the removal of fluid. A perfect "anti-fat" should increase the consumption of fat without at the same time exaggerating protein-breakdown. Thyroid, as we have seen, does not do this. This action of thyroid is probably peripheral, because the post-mortem breakdown of tissues under antiseptic conditions (autolysis) goes on more rapidly in the presence of thyroid extract. One milligram of thyroxin increases the metabolic rate of an adult by about 2 per cent., but when the imino-hydrogen of the molecule is displaced the substance becomes inactive. Increased rate of metamorphosis in the tadpole is brought about not only by thyroxin, but by many iodine derivatives and by iodine, but only thyroxin has the specific effect on metabolism and is specific for myxœdema and cretinism.

Circulation.—The most constant effect of thyroid-feeding is acceleration of the heart, and no explanation of the action is as yet forthcoming. It is possible, however, that some of the effects on the circulatory and nervous systems may be due to the increased tissue-breakdown and the liberation of purine derivatives.

Contrary to what has been generally stated, there is no effect on blood-pressure. The fall of pressure which occurs when decoctions of the gland are injected is due to organic extractives, and there is no effect on the blood-pressure when the drug is given by the mouth. Medicinal doses of thyroid lead to a relative increase in the number of the lymphocytes. The excretion of urine is augmented apparently on account of the largely increased excretion of urea.

Symptoms of thyroidism are very variable; sometimes large doses have no effect, while small doses may give rise to headache, wandering pains, and weakness. The most characteristic effects are a very rapid pulse, often associated with palpitation, alimentary symptoms, such as loss of appetite, nausea, and diarrhœa, fine tremors, perspiration, and a slight rise in temperature, the last being directly due to the augmented metabolism. Thyroidism occurs more frequently in those suffering from myxœdema than in normal people.

In cases of simple goitre the hypertrophy of the thyroid is a physiological response to a great demand for the secretion. This explains the remarkable diminution which certain of them undergo after thyroid feeding. Also, simple goitres are often greatly diminished by a course of iodides, and we know that these drugs increase the amount of iodine present in iodothyrin, which, in some cases at least, is thereby rendered more active.

Graves' disease or exophthalmic goitre is aggravated by thyroid treatment; and we have reason to believe that one feature of this disease is a hypersecretion from the gland. All the symptoms of thyroidism are present, with exophthalmos. The latter sign can be produced by experimental thyroid feeding, but not to any very marked degree. The effects of the drug on the eye—proptosis, dila-

tation of the pupil, widening of the palpebral fissure—erection of the hair, acceleration of the pulse, are such as can be produced by sympathetic stimulation.

Besides myxœdema cretinism is benefited by thyroid treatment; this is especially the case if the patient is treated early; his intellect improves, his growth is augmented, and he loses much of his deformity. Chronic psoriasis is sometimes cured by a course of this treatment, probably by the action of the drug on metabolism.

MATERIA MEDICA

Thyroideum Siccum.—A powder prepared from sheep's thyroid. **Dose, ½ to 4 grs.** (3 to 25 ctgrms.).

PARATHYROID GLANDS

The parathyroid glands in development and function are entirely independent of the thyroid, though related to it anatomically. Their extirpation in man and animals leads, after a latent period of two or three days, to fibrillary contractions beginning in certain muscles: the fibrillation changes to spasms, more and more muscles become affected, and the condition known as tetany is produced.

Men suffering from tetany and animals after parathyroidectomy show the same spasms and twitching of muscles; in both the urine contains an excess of guanidine, and in both there is a condition of hypoglycæmia. The administration of guanidine leads to identical symptoms, and the proof seems clear that tetany is caused by an excess of guanidine in the blood. The effects of administering parathyroids are not defined, but metabolism and especially calcium metabolism is influenced: it is found, for example, that varicose ulcers rapidly heal under this treatment.

PITUITARY EXTRACT

The pituitary body consists of three parts: (1) the pars anterior, formed of glandular epithelium; (2) the pars intermedia, formed of epithelium secreting a colloid material; (3) pars nervosa, consisting mainly of neuroglia.

The function of the pars anterior is probably related to growth, and when this part is hypertrophied in life the condition known as acromegaly is produced. The most characteristic sign of this disease is the increased growth of certain parts of the skeleton, especially the lower jaw and extremities of the limbs, with hypertrophy of connective tissue: the enlargement of the hands and feet is often the first marked sign.

The function of the pars intermedia is to produce a colloid material containing hormones acting upon the circulation and kidneys.

Circulation.—Extracts of the posterior lobe of the pituitary body tend to contract blood-vessels throughout the body, but different vessels are affected in very different degrees without any relation to their innervation, thus the pulmonary and coronary vessels constrict decidedly, as well as the splanchnic vessels. This is in marked contrast with adrenalin. The extract tends to constrict renal vessels considerably less than the other vessels, so that when the organism is under the influence of this hormone the kidney volume is increased as regards its blood-content, because

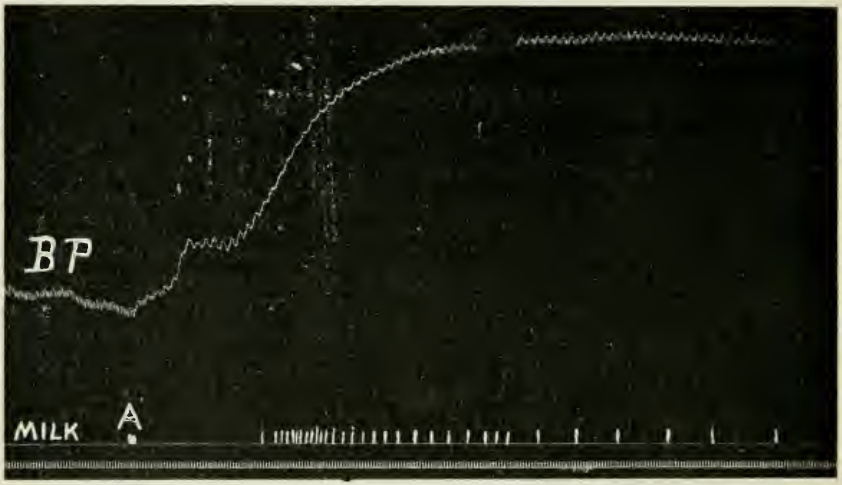


FIG. 91.—RECORD OF BLOOD-PRESSURE, AND MILK-FLOW IN DROPS FROM ONE NIPPLE OF A LACTATING CAT.

Shows the effect of injecting at A pituitary extract. Time = secs.

the general rise in blood-pressure to which the vaso-constriction gives rise overcomes the very slight tendency of the renal vessels towards constriction. Pituitary extract has been used to raise blood-pressure in cases of shock and collapse.

Plain Muscle.—The isolated uterus is sent into tonic contraction by pituitary extract, no matter whether it is pregnant or not; this again is in contrast with adrenalin. Its use has been recommended in obstetric complications associated with uterine atony. During the second stage of labour pituitary extract acts differently from ergot, in that it increases the pains of expulsion without altering much the permanent tonus, whereas ergot increases the tonus also. The pituitary gland enlarges during pregnancy, and it has been

suggested that the active constituent of the infundibulum is the hormone which starts normal labour.

The plain muscle of the spleen is also powerfully contracted, but the effect on the intestines and bladder is relatively small.

Kidney.—Pituitary extract causes distinct diuresis even on second and third injections, when there is little or no rise of blood-pressure. It is not yet decided whether this specific action on the kidney is upon the renal cells or whether it is the result of a redistribution of the blood in the system. The active principle is excreted in the urine. In diabetes insipidus injections of pituitary greatly diminish the thirst and the secretion of urine: the effect of each injection, unfortunately, only lasts six or eight hours.

Mammary Gland.—Injections of the posterior lobe cause an immediate and decided increase in the milk-flow in lactating animals. It is not possible, however, to increase the total secretion in a milch cow, nor is the amount of fat increased. It is possible that this action may be caused by contraction of the plain muscle in the mammary gland (Fig. 91).

SERUM THERAPY

If bacteria are grown in broth they produce in many cases poisonous bodies, probably of a protein nature, which can be separated from the bacteria by filtration, and to which we give the name toxins. When these toxins are injected into living animals, they give rise to the same effects as injections of the actual living organism from which they are derived. Not all bacteria have this property of secreting toxins; diphtheria and tetanus bacilli produce a plentiful supply of toxin, but others, like the pneumococcus, possess this power very slightly; nevertheless, they may be very toxic in virtue of their power of multiplying in the tissues. Immunity to toxins or to bacteria may be natural or acquired. All animals exhibit a certain degree of natural immunity, large in some cases and small in others, and this may be increased to a small extent by the injection of any protein substance, or even of sterile broth. By such means it is possible to avoid death in animals poisoned by the subsequent injection of a minimal fatal dose of bacteria or their toxins. We are concerned here with artificial immunity, which is of a specific nature, only protecting the animal against the particular organism to which it has been immunised.

Artificial immunity is concerned with the production of certain "anti" bodies in the blood; these are of two kinds: *antitoxins*, which chemically neutralise the toxin, and *antibacterial* bodies, which attack the bacilli and prevent their growth.

Antibacterial substances possess the power of dissolving and

destroying the corresponding bacteria. This power is lost by heating to 55° C. or by keeping for eight days, but is regained on the addition of a fresh quantity of serum. A normal guinea-pig dissolves a certain number of living cholera bacilli injected intraperitoneally, and the fresh serum of this animal also exerts a similar effect. This power is ascribed to "alexins." If the guinea-pig is made immune to cholera its antibacterial properties are enhanced: if now some of its serum is injected into a second normal guinea-pig, the power to dissolve very large quantities of cholera bacilli is also transmitted, that is, we have a specific bactericide.

Antitoxins are produced by injecting susceptible animals with living cultivations of the bacterium or, better, its toxin. The injections are small at first, but must be repeatedly increased until the desired degree of immunity is attained: the immunity results from the formation of antitoxin. Ehrlich has devised an hypothesis known as the side-chain theory to account for the production of anti-bodies. He considers that those cells, generally of the central nervous system, which are attacked by toxins possess an arm to which the toxin can attach itself, forming a side chain. After the injection of several doses of toxin, these arms tend to increase in number, the supply more than meeting the demand necessary to satisfy the toxin; in this case the arms are thrown off and occur free in the body fluids as antitoxin. In Chapter I. we have already seen that toxin and antitoxin combine together chemically and form a non-toxic substance.

Let us try to obtain a simple conception of what is going on in the living cell during antitoxin formation. If a small quantity of toxin is injected into the system, it combines with some substance generally in the brain. This we know, because, if a mixture of brain-emulsion and toxin is made outside the body and the resulting emulsion is injected into another animal, no poisonous effect is produced; the toxin is neutralised. We must, therefore, assume that, in the cycle of co-ordinated chemical changes (fermentations) which make up the life of the cell, one product has the power of combining with toxin.

If we take any simple fermentation and arrange matters so that the supply of fermentable material, as well as the products of the process, are kept constant, then the fermentation proceeds regularly and evenly: if now we remove the products of the action more rapidly, the fermentation is at once stimulated. This, we believe, is what takes place in antitoxin production. The toxin combines with the normal antitoxin, removes it from the sphere of action, and so leads to an exaggerated formation of this substance in a way analogous to the increased production of alcohol during sugar fermentation, which can be brought about by removing some of the alcohol.

Immunity to disease may be acquired in the following ways:—

(1) By a previous attack of the disease.
(2) By the injection of attenuated cultures, and, later, of virulent cultures.
(3) By the gradual injection of toxin.
(4) By injection of antitoxin.

Diphtheria Antitoxin

To obtain antitoxin it is first necessary to prepare a toxin. This is done by growing a suitable variety of diphtheria bacillus in broth: after some weeks' growth the broth must be filtered, and ought then to contain a good supply of toxin, so that at most $\frac{1}{10}$ c.c. should kill a guinea-pig. The sterile toxin is then injected into a horse, beginning with a dose of $\frac{1}{4}$ c.c., and gradually increasing up to several hundred c.c. as the horse becomes immune. After some months' treatment in this way the horse is bled to about eight litres, and the separated serum collected in sealed tubes, with a small amount of carbolic acid to prevent decomposition.

The standardisation of all forms of antitoxin is absolutely necessary; and the unit generally employed for this purpose is the quantity which completely neutralises one hundred fatal doses of toxin to a guinea-pig of about two hundred and fifty grams weight. The strength of antitoxin as commonly sold varies from four hundred to three thousand units per c.c. of antiserum. These drugs must always be injected subcutaneously; an average dose is five thousand units, and the amount which it is decided to give in any case of diphtheria should be injected during the first twenty-four hours.

The results of this treatment are:—(1) To prevent further exudation and to hasten the absorption of that which is present; (2) to improve the general condition of the patient, especially the pulse, to diminish swollen glands, and, above all, greatly to diminish the mortality.

Diphtheria toxin injected into animals causes cloudy swelling and fatty degeneration of the heart. But these changes are not produced if antitoxin is injected soon after the toxin. When the heart-muscle is once affected, the antitoxin has little beneficial effect, and hence the importance of injecting antitoxin early before degenerative changes have had time to develop.

Certain untoward effects known as serum sickness may be produced by the serum and not by the antitoxin itself. They are:—(1) Rashes in about 35 per cent. of the cases; these occur during the first week and are generally erythematous, more rarely papular or urticarial; (2) pains in the joints; (3) slight pyrexia; (4) septic troubles (avoidable); and, last, (5) collapse, which is extremely rare and the only serious complication (avoidable). *See* Anaphylaxis.

Dose.—500 units for prophylactic purposes. 2,000 to 6,000 units in early and mild cases. 20,000 to 60,000 units in severe cases.

Tetanus Antitoxin

Tetanus toxin as usually obtained is very powerful, so that an injection of even one-thousandth part of a cubic centimetre of a filtered broth cultivation is sufficient to kill a guinea-pig. If the toxin is injected into an animal, it is slowly absorbed through the motor nerve-endings, passes gradually up the nerves to the brain and cord, and not until it reaches these does it produce its typical action. It increases the reflexes, and gives rise to convulsions which have some resemblance to those of strychnine poisoning. The muscular contractions begin near the seat of injection, that is, they travel up the nerves from the nerve-endings nearest the seat of injection, and so affect the central cells from this area before the other parts of the central nervous system.

Tetanus antitoxin has not been such a success during the active disease as was anticipated. First, because the disease is not recognised until convulsions occur; in other words, until actual lesions have been produced in nerve-cells; and, secondly, because the antitoxin does not obtain access to the cord and brain, for, unlike toxin, it is not absorbed by the motor nerve-endings. Even rabbits whose blood has been rendered powerfully antitoxic by the previous subcutaneous injection of serum contain no antitoxin in their central nervous system, because if an injection of toxin is made into their brain it produces typical tetanic convulsions. When, therefore, tetanus is fully developed, the serum must be administered by slowly injecting it into the brain substance through a hole drilled in the cranium over the centre of the motor area.

The injection of tetanus antitoxin as a prophylactic measure, in certain injuries, such as those caused by shells and gunshot, has proved invaluable.

Antivenomous Serum

Animals can be immunised to snake poison by injecting sublethal doses at first, which are gradually increased. A horse can thus be rendered immune and an antitoxin prepared in the ordinary way. The serum is successful in the human subject if it is injected sufficiently soon after the bite.

Rabies

If the spinal cord of an animal which has died of rabies is allowed to dry for twelve days, and is then made into an emulsion, its injection into rabbits no longer produces death from rabies. Pasteur's treatment of this disease consists in the injection of emulsions of such cords taken from rabbits. After the cords have been allowed to dry the requisite number of days, they are emulsified with a little sterile broth and injected under the skin of the patient's abdomen. The treatment, therefore, is prophylactic and not

curative; it only acts by preventing the development of rabies. Other sera of more doubtful value are antityphoid (bactericidal), anticholera, antipneumococcic, and antitubercular.

Pollantin

Pollantin is an antitoxin employed in hay fever. It is prepared by making an animal immune against certain toxins which are present in the pollen of grasses. The antitoxin is applied directly to the nostrils of those suffering from the disease, and brings relief in a considerable proportion of cases.

Vaccines

The injection of sub-lethal doses of bacteria or their toxins into normal animals induces an increased resistance, which is termed acquired immunity. Vaccination consists in the injection of a small dose of dead bacteria or their toxins into a patient already suffering from a disease caused by a like organism to that in the vaccine. Many methods of vaccination are available, but the most general consists in the subcutaneous injection of the dead bodies of bacteria : for this purpose it is best to use an autogenous vaccine—that is, one prepared from the strain of bacteria producing the infection of the patient. The vaccine should consist of a pure growth of the organism diluted to a known strength, the organisms being killed and the emulsion of bacteria rendered sterile by heat.

Proof is still wanting that increased resistance can be conferred in disease by injecting the corresponding dead bacteria under the skin. It is clear that in general infections little advantage is to be gained by vaccination—that is, adding to the tissues already saturated with toxin an additional dose of poison. Vaccination has been carefully tried in bovine tuberculosis and pronounced a failure. In the special case of the gonococcus in gonorrhœal arthritis, Stockman, in a number of carefully selected cases, has shown that treatment by vaccination alone gives little or no benefit to the patient, but that by routine treatment with copaiba recovery occurs in from five to eight weeks. In chronic and localised staphylococcic infections this method of treatment may be of value in some cases, but no reliable statistics are yet forthcoming and very little experimental work has been performed.

It is well to recognise that treatment by vaccination is not a general law, and that in all probability its application in the future will be strictly limited.

VITAMINES

Proteins, fats, carbohydrates, salts, and water alone are incapable of maintaining life; something else is required, the chemical nature of which is unknown, but to which the term vitamine has been given.

When chemically pure proteins, fats, carbohydrates form a diet, health deteriorates, and in the young, growth ceases: if the diet remains unchanged, death results. Health can be re-established immediately if a natural food such as a little milk is added to the diet. Natural foods contain all the factors necessary for the proper growth and maintenance of the body.

Several vitamines probably exist; three are known and may be distinguished by their solubilities, their resistance to heat and other agents, and by their physiological properties. When vitamines are deficient disease occurs; three such deficiency diseases are known —beri-beri, scurvy, and rickets.

One type of vitamine is contained in the embryo of cereals. If milling is carried to a high degree this portion of the grain is removed, and therefore polished rice and superfine wheat flour would be vitamine-free. Beri-beri, the disease of rice-eating nations, is due to the use of polished rice and can be prevented or cured by adding the polishings to the diet. It is usual to speak of this vitamine, on account of its solubility in water, as "water-soluble B."

A second is contained in most animal fats and is abundant in milk and cod-liver oil. It is concerned with growth and therefore indispensable for the young. It is not present in vegetable fats. This vitamine is called "fat-soluble A," and its deficiency is a factor in the causation of rickets. Both "water-soluble B" and "fat-soluble A" are present in high concentration in the green parts of plants.

A third vitamine is known as "water-soluble C." This is the antiscorbutic principle, and is found in the juices of fruits, particularly the orange and lemon, and in most edible vegetables. It is extremely labile, being destroyed by moderately high temperatures, alkalies, desiccation, canning, and the like, whilst cooking seriously diminishes the amount present. Canned vegetables recover their antiscorbutic property if they can be germinated before being eaten.

ANTAGONISM

By antagonism we mean the counteraction of one drug by another. The antagonism between many drugs is easy to understand, and we have already had several examples. Thus, the acids are antagonised by the alkalies, calcium by citrates, and arsenic under certain conditions by freshly dehydrated ferrous sulphate. The antagonism in these cases involves simple and well-known chemical reactions.

The antagonism between drugs which exert a specific action of an opposite kind on a tissue is much more difficult to explain. Such drugs are rarely mutually antagonistic to one another, but a few examples of mutual antagonism exist. Spermine, an extractive which occurs in most tissues, diminishes the force and fre-

quency of the frog's heart; and atropine brings back the original condition. Further applications of spermine again weaken and slow the heart, and atropine reproduces the original beat. Or veratrine and potassium are mutually antagonistic to muscle. Veratrine applied to the skeletal muscle of a frog greatly prolongs the curve of relaxation. The application of a dilute solution of potassium chloride soon causes the normal muscle-twitch to reappear. Or, if the muscle is first made very feeble with potassium chloride, veratrine salts will bring back the strength of contraction. Physostigmine causes in mammals fibrillary twitchings of the voluntary muscle which still occur after section of the motor nerves, but not after the administration of curare. This curare paralysis can be relieved by physostigmine almost completely. These two drugs obviously, then, form an excellent example of mutual antagonism: curare stops the physostigmine twitchings, and physostigmine relieves the curare paralysis.

More usually, antagonism between two drugs is not mutual. Thus, atropine is antagonistic to pilocarpine, but pilocarpine is not necessarily antagonistic to atropine. In different dogs a constant amount of atropine is necessary to oppose the action of a constant amount of pilocarpine, and in the same dog the ratio of the two drugs remains the same, irrespective of how the actual amounts injected may vary. It appears, therefore, that the antagonism proceeds according to the laws of mass action rather than those of simple chemical combination in definite proportions.

It has been already pointed out that physiological action is sometimes determined by chemical combination of the drug with some dead constituent of the living cell. In this process the drug may be destroyed (secretin, adrenalin, and perhaps morphine). It is clear that there must be several positions in a cell upon which a drug may act. To illustrate this point, let us take one structure, the third nerve and circular muscle of the eye. In this system we are able to touch upon at least three points at which drugs may act. (1) Physostigmine constricts the muscle by exciting what we may call the nerve-endings. By extirpating all the ganglion-cells connected with this nerve, and allowing time for the nerve to degenerate, we abolish the effect of physostigmine on the muscle. (2) But pilocarpine, a drug which is usually regarded as acting on the same point as physostigmine, still produces constriction, and therefore cannot act in the same way. (3) Atropine acts either at some point peripheral to the pilocarpine, for minute amounts of atropine antagonise very large amounts of pilocarpine, or, as is much more probable, at the same point. (4) Barium or veratrine act more peripherally than any of these, and produce constriction equally well on the atropinised as on the normal eye.

The degree of antagonism between atropine and pilocarpine depends on their relative concentration in the organ on which they act; that is, the antagonism is subject to the law of mass action

and not to that of multiple proportion as in a chemical reaction. We have already pointed out the importance of this concentration factor in the case of anæsthetics and digitalis.

We may now turn to some examples of physiological antagonism.

On *striped muscle* we have the antagonism of potassium, fatigue and cold, to drugs like barium and veratrine, which augment the strength of contraction and prolong the relaxation. The latter drugs act by increasing katabolism, and thereby inducing a prolongation of the period of active contraction. Potassium and fatigue, by reducing the amount of substance capable of katabolic change, counteract the effects of veratrine. On *plain muscle* the best example is, perhaps, that of the nitrites and barium on the vessels. The nitrites depress muscle-fibre and so dilate the vessels, barium excites the muscle and so tends to constrict the vessels; but whether the two drugs act on the same constituent in the muscle-fibre it is impossible to say. On *cardiac muscle* such drugs as chloroform, chloral, and potassium diminish the force of contraction and increase the relaxation, whilst barium and veratrine, on the contrary, increase the force of contraction and diminish relaxation. Hence, these drugs are antagonistic to one another. On such an organ as the heart many drugs produce antagonistic effects without acting on the same structure: aconitine and caffeine, by stimulating the excito-motor area, quicken the heart, and this effect is in a limited degree antagonised by pilocarpine, which excites the vagal endings. Or the effect of a big dose of pilocarpine, which tends to slow the heart through the vagus, is annulled by an injection of adrenalin, which quickens the heart through the accelerator nerve.

The antagonistic action of drugs on *nerve-endings* is best illustrated by that of atropine and pilocarpine. Pilocarpine produces slowing of the heart, a copious flow of saliva and sweat, constriction of the pupil, and increased movements of plain muscle generally. These effects are antagonised in each case by atropine, which paralyses some portion of the nerve-endings, thereby interfering with the action of the former drug. Physostigmine, which has many effects resembling pilocarpine, is also antagonised by the atropine group of drugs. Again, digitalis excites the nerve-endings in the vagus, and so tends to slow the heart and to increase the peristaltic movements of the alimentary canal. These effects are also antagonised by atropine. And, lastly, adrenalin excites the nerve-endings of the sympathetic; apocodeine paralyses these same nerve-endings, and so abolishes the adrenalin effect. Ergotoxin paralyses those structures which adrenalin stimulates. So that where the nerve-supply from the sympathetic system is purely inhibitory ergotoxin is without action either on the adrenalin effect or on sympathetic nerve stimulation (stomach, intestines, gall-bladder). If the sympathetic supply is purely motor the action

of adrenalin or nerve stimulation is annulled (heart, dilator iridis, retractor penis, pilo-motor muscles, and ileo-colic sphincter). And if the sympathetic supply is mixed, ergotoxin removes the motor effects and leaves the inhibitory (the arteries of carnivora, spleen, uterus, &c.). Ergotoxin clearly, then, has a very specialised selective action on the motor elements of that structure, which is excited by adrenalin and by impulses in fibres of the true sympathetic system, the inhibitor elements being unaffected. The motor effects of pilocarpine on the pregnant uterus are antagonised by ergotoxin injected previously, whilst the inhibitory action is unimpaired, and in this pilocarpine resembles adrenalin ; but the pilocarpine effect is completely antagonised by atropine, whilst the adrenalin action remains uninfluenced, and, further, not only is the motor action of pilocarpine abolished by atropine, but its effects on the inhibitory functions also disappear. The relative degree of contraction or relaxation that pilocarpine produces on the uterus varies exactly with that produced by stimulation of the hypogastric nerves. As examples of drugs acting in the opposite direction on *motor nerve-endings*, we have physostigmine and aconitine on the one hand, which produce twitchings of the muscles : these are not affected by section of the nerve, but they are eliminated by curare, which paralyses the motor nerve-endings. Again, aconitine and veratrine excite *sensory nerve-endings* and give rise to tingling and pain, whilst cocaine paralyses some portion of the peripheral sensory mechanism, thereby annulling their effects.

Our whole knowledge of " nerve-endings " is, however, very limited. For example, the proof that physostigmine acts on motor nerve-endings and causes muscular twitchings seems clear enough, yet we do not understand why this action is antagonised by atropine and calcium, two drugs which, so far as we know at present, do not influence these nerve-endings.

There are many examples of drugs producing opposite effects on *nerve-cells*. Nicotine, coniine, and lobeline stimulate the sympathetic nerve-cells, whilst apocodeine paralyses these cells. On the spinal cord we know that strychnine has an effect on some portion of the sensory apparatus which gives rise to increased reflexes. Chloral, urethane, or alcohol diminish reflexes by acting probably on the same structure. Indeed, a large dose of urethane has such an effect that strychnine is no longer capable of inducing convulsions. The medulla is excited by such drugs as picrotoxin and aconitine, and hence the tonic action of the respiratory, vasomotor, and vagal centres is increased. But chloral or chloroform, by depressing the centres, counteracts the effect of these drugs.

On the brain we know that caffeine excites the psychical or higher centres, and that cocaine, atropine, and absinthe excite the motor areas. Alcohol and the hypnotics, by depression, counteract the former, and all hypnotic substances depress the motor areas.

In all these examples which we have mentioned it is always

the paralytic drug which is antagonistic to the stimulant, and never *vice versa*. Other examples of antagonism, such as the action of calcium against leech extract, and of toxin towards antitoxin, are considered elsewhere.

Finally, before leaving the subject, it should be mentioned that certain crude drugs contain active principles which are antagonistic to one another. Physostigmine depresses the central nervous system; calabarine, also said to be present in the bean, has a strychnine-like action. Digitoxin excites cardiac muscle and stops the frog's heart in systole. Digitonin has an opposite effect and stops the heart in diastole. Morphine depresses the central nervous system; narcotine, and more especially thebaine—other constituents of opium—produce convulsions.

RADIO-THERAPY

Various kinds of rays are now used to influence the body tissues—sunlight, ultra-violet (Finsen), X rays, and radium emanations.

The salts of *radium* are continually giving out rays which are of three kinds:—α particles, which carry a positive charge and are easily stopped; they give off helium. β particles, which are more minute, carry a negative charge and correspond with cathode waves; they penetrate well and pass through thin layers of metal. γ or X rays; these penetrate considerable thickness of metal.

When living cells, especially young or growing cells, cells of embryonic type, cells of the sexual organs or pathological new growths, are exposed to rays of any kind their activity is at first increased; later with larger doses it is diminished and death may follow. Treatment with rays of various kinds has proved valuable in certain skin affections such as rodent ulcer and lupus, but in the treatment of deep-seated affections difficulties are encountered with regard to penetration and localisation.

Ultra-violet rays destroy not only living protoplasm but ferments also, and they are used in cancer and lupus for their destructive action, the rays being concentrated by the Finsen method.

One property of fluorescent substances is to absorb luminous energy, and the power of acridine to destroy organisms in the light we have already noted. If $\frac{1}{2}$ per cent. solution of eosin, which is also fluorescent, is painted on the skin and exposed to sunlight a corrosive effect is produced.

X rays have a pronounced effect in destroying leucocytes, and are sometimes used in diseases such as leucocythæmia, in which the leucocytes in the peripheral circulation are greatly augmented (Fig. 92). The inhalation of benzene produces a similar disappearance of leucocytes.

It has been stated that some radio-active salt is necessary for all normal function. One example will make this clear.

Potassium is the only element essential to life which possesses radio-activity. A frog's heart perfused with Ringer's solution ceases to beat when it is deprived of potash, but beats again when an

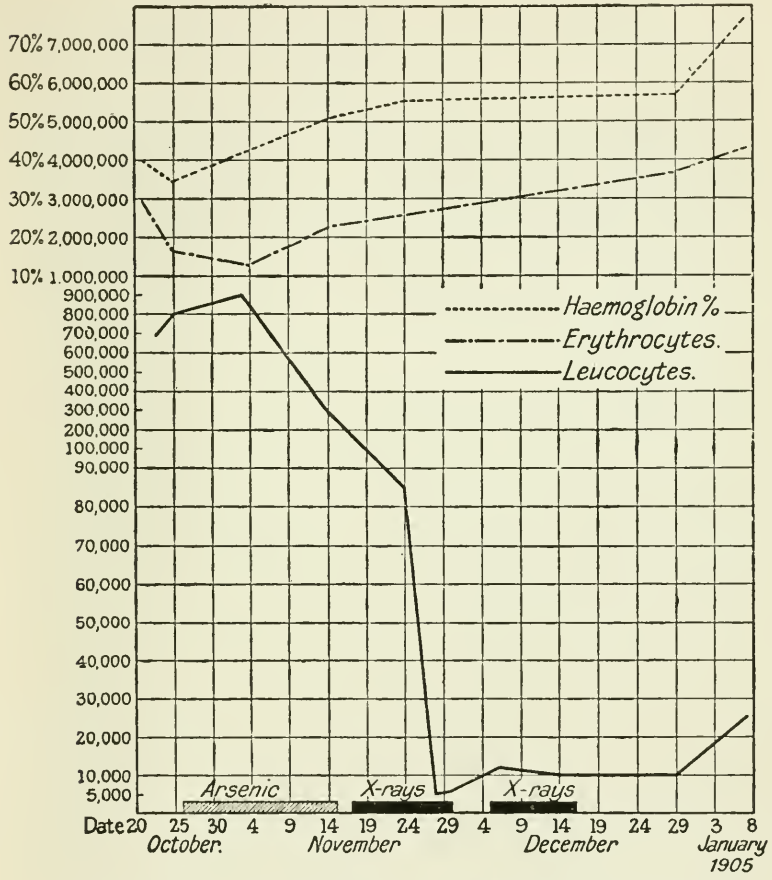


FIG. 92.—E. W., AGED SIXTEEN. SPLENOMEDULLARY LEUKÆMIA.

Shows the effect on blood of administering arsenic and X rays. (Abram.)

equi-radio-active amount of another element is added to the perfusing fluid to replace the potash, or even by exposing the heart to the β rays of radium.

The following table shows a list of such radio-active elements which it has been claimed may be substituted in appropriate amount for potassium.

I.	II.
Emitting – β Rays.	*Emitting + α Rays.*
Potassium.	Uranium.
Rubidium.	Thorium.
Cæsium.	Radium (some β, but α predominate).

Considerable doubt exists as to whether the members of Group II. can be substituted efficiently for those of Group I., and in any case it has yet to be determined whether it is the absorption of the electrical charge which is the important factor in these cases.

INDEX

PRINTED IN GREAT BRITAIN BY
BILLING AND SONS, LTD., GUILDFORD AND ESHER