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THE THYROID GLAND

IN HEALTH AND DISEASE

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BY

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TO

MY WIFE

Nil sine te mei
prosunt labores

PREFACE

A PERIOD of sick leave from active service has afforded me an opportunity to incorporate into one volume the results of some fourteen years of study of the thyroid apparatus and its diseases.

When, in 1902, I undertook the investigation of the ætiology of its maladies a maze of hypotheses and uncertainties surrounded the subject. Knowing nothing, premising nothing, I determined to examine it from the combined epidemiological, clinical, experimental and pathological points of view. Some years of extensive epidemiological research cleared the ground of many false hypotheses, resolved some uncertainties, and brought to light certain facts which suggested an infectious or toxic origin for some of the thyroid's most common disorders. Clinical experience during the same period added further facts which strengthened this supposition; observations on man and experimental work on a large scale on animals converted the supposition into what I believe to be fact, and pathological studies have since confirmed my belief.

Meanwhile it became necessary to revert to the study of the normal thyroid gland in order fully to understand the various processes of abnormality. As a result of this study a number of important points relating to the gland's normal range of physiological action were elucidated, whereby it became possible to interpret the pathological changes to which various experimental procedures had given rise.

The epidemiological work received confirmation from the observations made on artificially-bred trout in America, by Marine and Lenhart and by Gaylord; the clinical and therapeutic facts were supported by the researches of Messerli; the earlier experimental findings were confirmed by Sazaki, working under Wilms of Heidelberg, by Gaylord in America, and by Messerli in Switzerland. Finally, the histo-pathological studies of the

human goitrous thyroid, carried out by Wegelin of Berne and by Marine and Lenhart of Cleveland, left little room for doubt but that the morbid process in the human subject was identical with that produced experimentally in animals.

The great fact which has emerged from these diverse but complemental methods of investigation is that the most common source of the thyroid's derangement is gastro-intestinal toxæmia—a fact which within recent years has received further striking confirmation from the surgical procedures of Sir Arbuthnot Lane.

The observed facts and the thoughts to which they have given rise form the framework of this book, and for its completion I have drawn from the work of others what my own observations have failed to provide.

In preparing it my object has been to present to the reader a simple and connected account of the place of the Thyroid Gland—with which I include the Parathyroid Glands—in the human economy, and of the disorders to which these organs are subject.

The work is divided into three parts: the first dealing with the Thyroid and Parathyroid Glands in health; the second with the factors which cause them to depart from health; and the third with the morbid states—including not only goitre and cretinism, but also tetany, myxœdema and Graves' disease—which result from this departure. In an appendix two series of cases, showing the effects of intestinal antiseptics on goitre, have been added, as well as a brief summary of the more important of my epidemiological and experimental observations. A list of my original papers, to which the bracketed numbers in the text refer, is also included in the appendix.

I desire to express my indebtedness to Lady Horsley for the use of figures 10, 21, 24, 59, 70–74, which are from specimens in the possession of the late Sir Victor Horsley, F.R.S.; to the Editor of the *Practitioner* for permission to use figures 30, 31, 33, 77, which appeared as illustrations to an article I contributed to a special number of that journal on "The Ductless Glands," in 1915; to the editor of the *Quarterly Journal of Medicine* for the use of figures 28, 29; and to the publishers of the *Journal of Tropical Medicine and Hygiene* for the use of figures 9, 51 and 52, from papers published by me in these journals. To Dr. Leonard

Williams I am indebted for reading my manuscript and for his courtesy in lending me figure 77; to Dr. John Thomson for permission to use the photographs of his cases shown in figures 60, 65, 66; and to Dr. Nathan Mutch for figure 76.

The later part of my researches was carried out under the auspices of the Research Fund Association of India (1913–1914), in whose official Journal a number of my papers were published in 1913–1915. My thanks are due to the Governing Body of this Association for permission to use figures 1–8, 11–14, 16–23, 25, 32,34, 49, 50, 53, 54, 67–69, 78–82 by which the papers were illustrated.

R. McCARRISON.

London,
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Unless otherwise specified, the illustrations are from originals prepared by the Author.

PART I

THE THYROID AND PARATHYROID GLANDS IN HEALTH

SECTION I

ANATOMY

The *Thyroid apparatus* consists, in man, of the thyroid gland proper, a variable number of parathyroid glandules, and in some cases of portions of thyroid tissue (accessory thyroids) lying anywhere in the region between the base of the tongue and the aorta.

It is probable that the *pars intermedia* of the pituitary body may have to be added as a third constituent of this apparatus, since, according to Swale Vincent, it appears to act as a substitute for the thyroid in case of the removal or atrophy of the latter.

In the exercise of its functions the thyroid apparatus is specifically associated with certain other hormone-producing organs: the generative organs, the liver, the pancreas, the supra-renal capsules, the pituitary body and the thymus gland.

While the anatomy of the thyro-parathyroid glands may be well known to every one who reads this book, these organs possess certain features a right appreciation of which aids in the clearer comprehension of their normal activities as well as of the abnormalities to which they are subject; I therefore make no apology for recapitulating.

The *Thyroid Gland* consists of two somewhat pear-shaped lateral lobes of reddish-brown colour joined together by an isthmus or median lobe. The lateral lobes are disposed on either side and in front of the larynx and upper three or four rings of the trachea. Their upper conical poles extend to the middle of the thyroid cartilage, their lower thick and rounded poles reach almost to the line of the sternum. The posterior edge of the left lobe extends back to the œsophagus.

The isthmus is absent in 15 to 20 per cent. of cases; as a

rule it is represented by a narrow band lying over the third and fourth tracheal rings, where it can be readily felt. It is in the isthmus that degenerative and fibrotic changes are liable to begin; consequently failure to detect it clinically may indicate commencing fibrosis. A projection—the *processus pyramidalis*—may extend upwards from the isthmus or either of the lateral lobes and be attached to the thyroid bone by a fibro-muscular band. The organ follows the larynx in deglutition, a fact of importance in its clinical examination.

The gland varies considerably in size and weight, its variations to some extent being dependent upon the age, sex, place of residence and state of general nutrition of the individual. It is relatively larger in infants than in adults, forming about $\frac{1}{800}$th part of the body weight in the former and $\frac{1}{1800}$th part in the latter. In the adult its average weight is 36–50 grammes in inland tracts and hilly districts, 20–30 grammes at the sea coast. It is roughly one-third heavier in females than in males.

In estimating the increase in size of the thyroid by measurement of the circumference of the neck, it is well to be aware of the fact that—in the absence of other factors—an increase of $\frac{3}{4}$ to 1 inch will represent a doubling of its volume, a further increase of $\frac{3}{4}$ to 1 inch a trebling, and a still further increase of $\frac{1}{2}$ to $\frac{3}{4}$ inch a quadrupling of the gland's volume. These figures are approximately correct for necks whose normal circumference is 13–16 inches.

The *Parathyroid Glands* are variable in number and in position. In about 80 per cent. of cases there are four, two being situated on either side of the median line of the body. The upper pair are usually embedded in the substance of the thyroid at its upper and posterior aspect; the lower pair are closely adherent to the posterior and external aspects of its lower poles, and close to the branches of the inferior thyroid artery and recurrent laryngeal nerve. The inferior pair, may, however, be situated much lower down; in rare cases they have been found as low as the tenth tracheal ring. In about 7 per cent. of cases in normal individuals there are five parathyroids; in 9 per cent., three, and in 2 per

cent., two. In shape they are oval or pyriform and of a yellowish colour owing to the presence of fat. Their average dimensions are 2 by 4 by 6 mm. ; their average weight 0·035 gramme.

Iverson found in a number of cases of goitre examined that two parathyroids were present in 4 per cent., three in 36 per cent., four in 56 per cent., and five in 4 per cent.

Blood Supply.—The thyroid is one of the most vascular organs of the body. It is estimated that in proportion to its size it receives more than five times as much blood as the kidneys, while nearly as much blood passes through its arteries as through the internal carotid and vertebral to the brain. Vasomotor dilatation, therefore, is capable of giving rise to rapid swelling of the gland.

The superior and inferior thyroidal arteries form a rich anastomosis on its surface, their smaller branches penetrating with the connective tissue framework between its lobes and lobules. Here they divide and re-divide until each individual follicle is surrounded by a close network of sinus-like capillaries with which the vesicular epithelium is in perfect contact.

The veins are correspondingly large and numerous, intercommunicating freely. They empty themselves into the internal jugular and innominate veins. They are valveless. A special branch of the inferior thyroid artery supplies each parathyroid ; a copious capillary network coming into intimate contact with its secreting cells.

Lymphatic Drainage.—The lymph system is very free. Lymph spaces lie outside the peri-vesicular capillaries. These peri-alveolar spaces join with interlobular vessels forming large trunks which anastomose into plexuses lying beneath the capsule of the organ. From these plexuses two main trunks convey the secretion-containing lymph to the circulation by way of the superior and inferior deep cervical glands.

The lymph drainage of the parathyroid glandules is equally free, and joins the lymph system of the thyroid with the secretion from which organ it is intermingled.

Nerve Supply.—The thyroid apparatus receives its nerve supply through the superior and inferior laryngeal nerves, from the vagus and from the superior cervical ganglion of the sympathetic. Fibres are distributed to the muscle cells of the vessels and to the secreting epithelium. Its secretory fibres reach the cells from the cervical sympathetic so that the secretion of the gland is directly under the control of sympathetic impulses (Cannon). Cannon states that as the result of experimental stimulation the secretion issues as promptly as in 5 to 7 seconds.

The same observer has shown that when the phrenic nerve is joined to the peripheral portion of the cervical sympathetic in the cat, and the thyroid is thus continuously stimulated as the animal breathes, this operation results in tachycardia, increased excitability, loose motions, exophthalmos on the operated side, great increase in the metabolism, and in some cases an increase in size of the adrenals.

Development.—The thyroid gland is developed as a median evagination of the entoderm lining the floor of the pharynx at a level between the first and second branchial pouches. This outgrowth makes its appearance early and grows backwards as a small pouch which expands at the upper part of the trachea into two lateral wings. Its median stem becomes converted into a duct—the *ductus thyreo-glossus*—which gradually elongates with the growth of the embryo. In some of the lower animals—Tunicates, Amphioxus and Ammocætes—the connection of the duct with the buccal alimentary tube is retained, but in man it becomes obliterated, as a rule about the eighth week of fœtal life, its former opening at the base of the tongue being represented by the *foramen cæcum*. Occasionally the thyro-glossal duct remains patent, or incompletely obliterated, when it may become the seat of fistulæ, cysts or tumour formation.

The bi-lateral expansions of the epithelial outgrowth branch and re-branch, ultimately forming groups of small epithelial masses in which little closed epithelial-lined cavities are formed ; these constitute the vesicles or secreting units of the organ. These vesicles are formed by the breaking down of the central cells of

a given epithelial mass to form the colloid-content of the cavity, the peripheral cells of the mass forming the vesicular lining.

The majority of the ultimate cell masses combine to form the thyroid gland proper, but some may become detached from the main mass and wander downwards with the heart, situating themselves in various parts of the area lying between the root of the tongue and the aorta. In this situation these cell rudiments develop into thyroid tissue in all respects identical with the gland itself. They are known as *accessory thyroids*, and may give rise to " aberrant goitres " as, for example, *lingual goitres* and *retro-sternal goitres*. Accessory thyroids are most common in the neighbourhood of the tongue and the hyoid bone, but they may occur under the maxilla, behind the pharynx or œsophagus, in the vicinity of, or more rarely in, the larynx and trachea, near the crico-thyroid and aorta, and in the mediastinal regions (d'Aintolo).

The parathyroids are developed from the third and fourth visceral pouches and have thus a common origin with the thymus. Thymus rudiments are commonly found in the parathyroids and vice versâ.

Morphological studies have shown that the thyroid apparatus from the earliest period of its evolutionary history has been an essential part of the digestive tract (Marine) and so intimately related with the genital organs as at one time to have formed an integral part of them (Gaskell). In its most highly developed form in the human subject it still retains its fundamental function of profoundly influencing nutrition, growth and reproduction, and is itself profoundly influenced by disorders of the alimentary tract and genitalia.

SECTION 2

HISTOLOGY AND PHYSIOLOGY

Structure.—The following account of the structure of the thyroid gland is based on a study of over 350 healthy thyroids from wild rats [19]. The comparative anatomical studies of Marine, Lenhart and others have shown that the gland presents identical features in all mammals. Rats were selected by me for the purpose of determining the influence of various factors—age, sex, altitude, season—on the process of secretion in perfectly healthy glands in which the histological appearances were uncomplicated by the pathological changes inseparable from domestication in animals and man.

The *Thyroid Gland* is surrounded by a thin capsule of connective tissue from which processes, composed of white fibres and elastic fibres, pass into the gland dividing it into lobes. These processes carry with them the blood-vessels and nerves and they subdivide the lobes into smaller and smaller lobules. Scattered throughout these lobules are large numbers of closed vesicles each enveloped in a very fine and highly vascular fibro-elastic covering.

The vesicles, which are the secreting units of the gland, vary much in size and shape. They are small in the glands of the newly-born and young, while in the adult they are smaller towards the centre of the gland—larger towards its periphery (fig. 1). In the adult their size varies from 45 to 300 μ. In shape they may be rounded, long, oval, polyhedral, or occasionally tubular. Sometimes they have side branches, or several vesicles may intercommunicate.

In health each vesicle is lined by a single layer of epithelium which rests directly on the vascular connective tissue envelope. There is no basement membrane. The vesicular epithelium varies in height from low cuboidal (9 μ) (fig. 1) to low columnar

(13 μ) (fig. 2), according to the state of secretory activity of the gland. The vesicles contain the *colloid substance* which is so characteristic of the thyroid, and forms more than half of its total bulk. When the organ is in the " resting stage " of secretion the vesicles are distended with colloid and the epithelium lining them is flattened out in proportion to the degree of distension (fig. 1). When, on the other hand, the gland is in a state of "active secretion" the vesicular cells are cuboidal or even columnar in form and there is but little colloid in the vesicles (fig. 2).

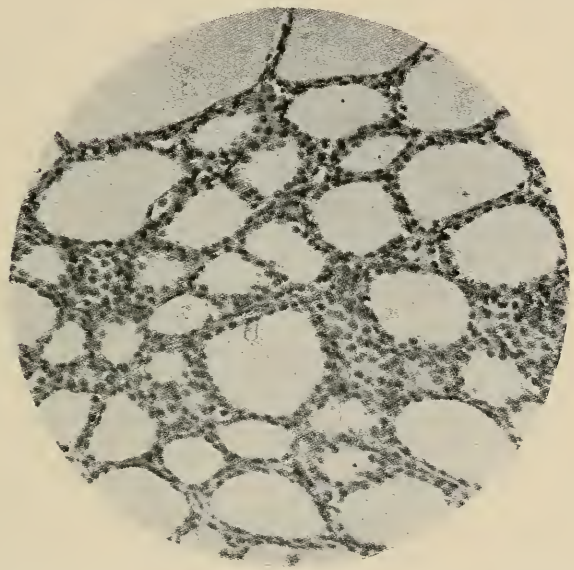


FIG. 1.—Section of normal thyroid of wild rat in colloid or resting state. ×250. Note flat vesicular epithelium and vesicles distended with colloid.

The protoplasm of the cells is retiform in structure and often contains highly refractive granules of varying size lying near the vesicular edge of the cell. The nuclei are spherical and show a fine chromatin network. Mitotic figures and recent division forms of nuclei are commonly to be seen in the glands of the new-born and young.

Lying between the vesicles and filling up the spaces left by the approximation of the more or less rounded vesicles is the intervesicular parenchyma. The cells in this situation are essentially the same in structure and in function as those lining

the vesicles. They are the reserve parenchyma cells from which new acini are formed as occasion may demand.

These cells also, if not actually identical with those of the parathyroid, are at any rate very similar to them in structure and appearance. The intervesicular parenchyma varies greatly in amount at different age periods. The fœtal thyroid is largely composed of it; it is plentiful in the new-born and in young subjects (fig. 3), but with advancing age the gland becomes less cellular and more vesicular. In the same organ some parts may be more cellular than others; some parts more vesicular than

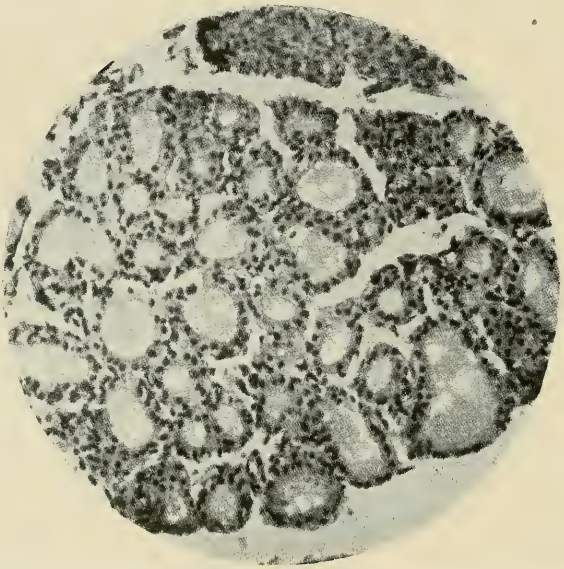


Fig. 2.—Section of normal thyroid of wild rat in state of active secretion. The *colloid* is undergoing absorption and newly formed *secretion* is being poured into the lymph spaces. ×250.

others. Occasionally the cavities of the vesicles are separated only by the two rows of cells forming their walls (fig. 1), and by the vascular network surrounding them; but much more commonly they are separated by a layer of cells of variable thickness (fig. 3). When the vesicles are small the intervesicular parenchyma is more plentiful; when they are larger it is correspondingly diminished. Two sections from the same gland may thus vary considerably in appearance.

Some authors divide the parenchyma cells of the thyroid into

" principal cells " and " colloid cells." Such a division is unnecessary and misleading since the different appearances represent different stages of the cell's activity. All parenchyma cells, whether lining the vesicles or not, may, if occasion demands, form themselves into new vesicles and take part in the formation of the gland's secretion. After death from acute infections or poisonings the cells lining the vesicles may become separated from their basal attachments.

The intervesicular tissue may, in addition to its parenchyma

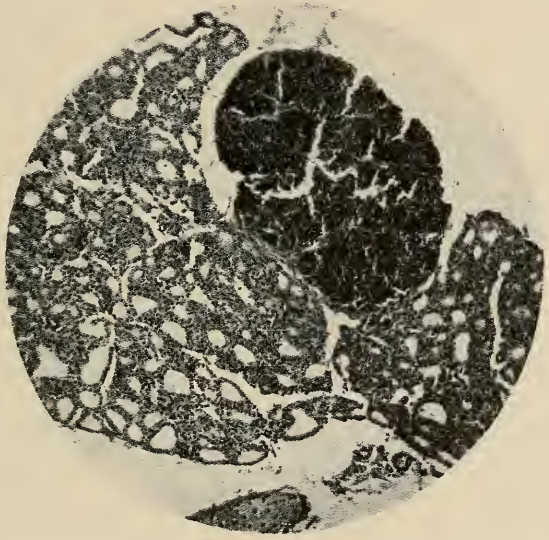


Fig. 3.—Section of normal thyroid and parathyroid of young adult wild rat, showing the proportion of intervesicular tissue to vesicles usually met with in young thyroids. ×100.

cells, contain portions of thymus tissue or of parathyroid tissue. Many small cells may be found scattered through it or arranged in masses. Some of these are lymphocytes, others, found in more compact masses, are the " fœtal rests " from which " fœtal adenomata " are said to arise.

The *Parathyroid Gland* is composed of polygonal epithelium-like cells. The cells may be disposed in a retiform manner and separated by an extremely delicate network of fibres (fig. 4) or they may be arranged in compact masses; both arrangements may be seen in the same glandule. Strands of connective tissue

from the areolar capsule of the gland, carrying with them the blood-vessels and nerves which supply the epithelium, divide the glandule into irregular lobules. These strands contain plain muscle and fat cells.

The parenchyma cells are of two kinds: the "principal cells," which are small with a homogeneous or somewhat granular

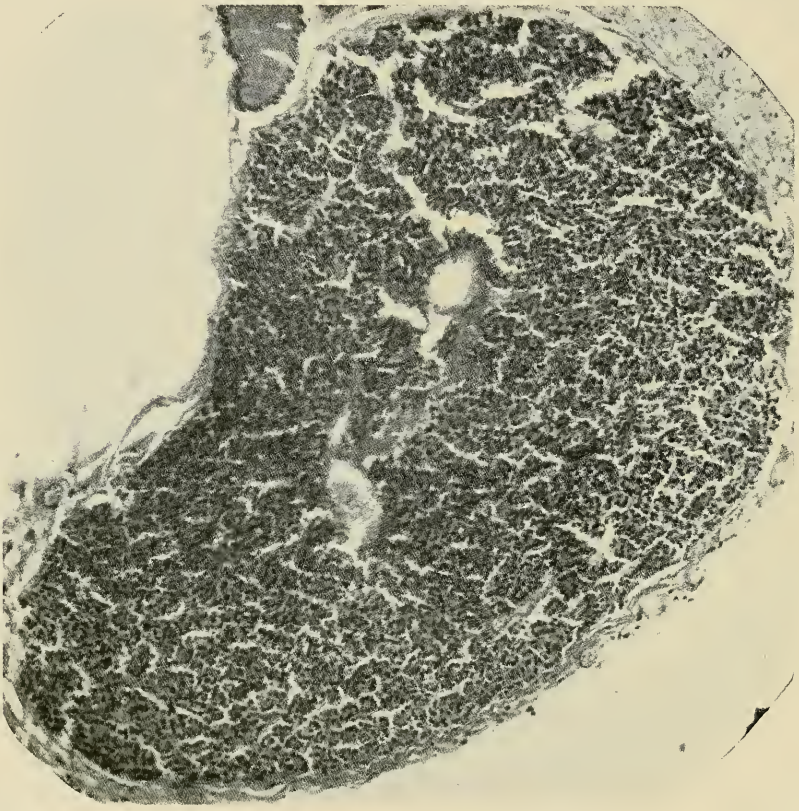


FIG. 4.—Section of parathyroid of wild rat showing usual arrangement of parenchyma cells and capsule of areolar tissue. ×200.

protoplasm, and other larger cells containing oxyphil granules staining with eosin; in man the latter only appear after the tenth year (Walsh). Both kinds of cells contain fatty granules which increase in number with age. They probably represent different stages of secretory activity of the parenchyma cells. Vesicles may be found in the gland containing a substance

resembling colloid, or more rarely colloid may be found lying between the cells. According to Vincent these vesicles increase in number with age and after complete removal of the thyroid.

Thymus nodules may be found in the parathyroid, just as may portions of parathyroid be found in the thymus, a fact which is explained by their similar development.

Process of Secretion.—The process of secretion in the human subject is difficult to study, owing to the lack of healthy thyroids of all ages available for such work. Persons who have died from diseases due to micro-organisms almost invariably show changes in the thyroid which mask the true picture of healthy secretory activity. It is more convenient, therefore, to study the process in healthy animals of omnivorous habits living in the wild state in which the changes are identical with those occurring in man. Such an animal is the wild rat, and a study of serial sections of over 350 healthy thyroids from those animals has shown that two well-defined phases of secretory activity are to be distinguished : *the colloid or resting phase* and *the phase of active secretion*.

In the colloid or resting phase (fig. 1) the acini are distended with a granular or perfectly homogeneous colloid. This substance lies closely applied to the lining epithelium unless a fixative has been used which causes shrinkage in addition to coagulation. In this event indentures at the edge of the colloid are to be seen. It shows few, if any, vacuoles. It stains freely with all aniline dyes, and, as a rule, uniformly ; occasionally, however, a denser area may be seen towards its centre. The protoplasm of the cells stains uniformly. The nucleus is placed either at the centre or at the base and may almost fill the flattened cell. It is spherical or oval in shape, according to the degree of flattening of the cell. It stains uniformly unless, as occasionally happens, it is vesicular. The vessels and capillaries of the organ are not distended.

This phase of thyroidal activity can be produced in animals at will by the administration of iodine or iodine-containing foods

(Marine). It is the stage in which the colloid has become thick owing to its gradual admixture with the elements of cellular disintegration, when iodine has been fixed by the colloid and the consistency of this substance has been altered by the salts of the body tissues. It constitutes a reserve of iodine-containing substance which is available for absorption and distribution to the blood as occasion may demand.

When such a gland begins to secrete actively the following changes occur: the vessels and capillaries become fuller. The colloid becomes vacuolated and gradually undergoes absorption, wandering leucocytes assisting in the process; the absorption is more rapid at the periphery of the colloid mass and a crenated appearance results (fig. 2). The vesicular epithelium heightens, becoming cuboidal or low columnar in type; the protoplasm is granular, and, on the discharge of these granules in the form of a thin secretion into the vesicle, or directly into the lymph spaces, it may appear pale and vacuolated. The nucleus is centrally placed and does not fill the cell. The edge of the epithelium towards the acinar cavity is uniform at first, but as the process continues it may become ragged and irregular in places, merging into the colloid substance. Leucocytes may wander into the acinus and become intermingled with the disappearing colloid. No increase of the stroma occurs, but the inter-vesicular tissue may appear relatively increased in amount owing to the emptying of the vesicles of their colloid-contents.

The fresh secretion of the cells is quite fluid or only slightly gelatinous and its staining is pale. It finds its way readily into the lymph spaces. This I have been able to observe only in the congenital goitres of goats where there was an enormous production of secretion. In these the thin secretion could be seen permeating the interstices between the cells and distending the lymph spaces. Presumably, therefore, the same route is followed in the case of the physiological process of secretion. It is only the thin, fresh secretion which reaches the circulation in this way, the store of colloid substance being used up by a process of solution and absorption. Towards the end of the process the secretion from the vesicular cells begins to accumulate in the vesicles, where

it becomes intermingled with portions of disintegrated cells and increases in viscosity in consequence probably of chemical change. This colloid substance then becomes impregnated with iodine in organic combination. Thus the gland returns to the " colloid " or " resting state," and the whole process is repeated in accordance with the needs of the body for iodine-containing thyroid secretion. In health the process stops short of the total expenditure of stored-up colloid, so that frequently small masses of this material are left behind in the vesicle around which the new colloid is deposited. The whole process has for its object the absorption of the reserve store of iodine-containing colloid and its distribution to the body cells in accordance with emergency demands.

I look upon the colloid as a substance designed to contain an emergency reserve of iodine, a reserve which is not ordinarily called upon in the daily routine of the body demands. The thyroid cells elaborate the specific hormone for the daily needs, probably from substances supplied to them in the blood without calling on this reserve. The " emergency ration " of iodine-containing colloid is, however, called upon when the supply of iodine in the food runs short, under the demands of excessive sympathetic excitation such as occurs in rage or fright (Cannon), at certain periods of life—dentition, puberty, menstruation, pregnancy or lactation, as a result of residence at certain high altitudes, at certain seasons of the year, and when the body is invaded by micro-organisms, or subjected to certain intoxications. In the event, however, of the operation of micro-organisms or intoxications the process goes beyond the limits of physiological demands, and pathological changes occur in the gland in consequence. These will be dealt with in their own place.

I consider that a distinction is to be drawn between the " thyroid secretion " and the " colloid," the latter term ought to be restricted to the reserve store of iodine-containing material. It is necessary to realize that the stored-up " colloid " is no measure of the state of activity of the gland at the time of its examination. This activity is indicated by the degree of parenchyma hyperplasia and by the amount of " secretion " lying between the cells and in the lymph spaces.

SECTION 3

CHEMICAL PHYSIOLOGY

Colloid is insoluble in boiling water, alcohol or ether; it coagulates after death and on treatment by heat or various fixatives: alcohol, inorganic acids, salts of mercury and other metallic salts, picric acid and osmic acid. Some of these cause shrinkage, while others, such as osmic acid mixtures, cause coagulation alone. It stains readily with eosin and other aniline dyes. Hæmotoxylin stains it less easily, giving to it a faint grey or greyish-violet tinge. Picrocarmine stains it yellow, while the epithelial wall is stained red. These stains show the colloid to be granular or homogeneous in structure. The staining capacity of the colloid varies with the phase of secretory activity of the gland. Fresh secretion stains feebly, old collections readily, varying in direct proportion to its iodine-content. Acetic acid and dilute hydrochloric acid cause the colloid to swell and render it transparent. Alkalies have a like effect, but greater in degree, causing deliquescence (Vincent).

On heating with strong nitric acid a yellow colouration occurs (Xantho-protein) which changes to orange on the addition of ammonia. Copper sulphate and potassium hydrate tinge the colloid violet (Biuret reaction).

These reactions indicate that the colloid substance is composed mainly of protein. It contains sodium chloride in abundance. It does not contain mucin nor any appreciable amount of globulin (Vincent). Cholin, lipoids and a lipolytic ferment have been found in it. It contains also, phosphorus, sulphur, arsenic, bromine and iodine.

The most important constituent of the colloid substance is iodine. Except in the thyroid of the fœtus and in the new-born, when iodine may be absent or exist only in small amount, it is

invariably present in normal human thyroid tissue (Cameron). Marked variations occur in the iodine-content of the gland not only in individuals of the same species but also in different species. The iodine-content of the food is the determining factor in these variations. Thus sheep pastured at the sea-coast, as in the Orkneys, show twice the amount of iodine in their thyroids as do those pastured inland (Hunter and Simpson). Generally speaking, herbivora, whose food contains a high proportion of iodine, show a high iodine-content in the thyroid; carnivora, whose food contains little iodine, show a low iodine-content, while in omnivorous animals the content is variable. In dogs, for example, Marine has found that the iodine-containing colloid may be made to disappear by feeding them on an exclusive meat diet. On the other hand, the same observer has noted that the colloid or resting state of the gland can be brought about by feeding animals on iodine-containing materials.

Iodine is present in many other organs and tissues of the body, as is to be expected where there is a circulation of this element in the organism. Thus it occurs in the centra nervous system, the lungs, the liver, the kidneys, the adrenals, the bile, the muscles, the spleen, the lymph glands, the hair, the glandular part of the hypophysis, the thymus, the nuclei of all cells. It is usually stated to be absent from the parathyroids, but some observers have detected it in these glandules also.

In no other organ or tissue, however, does it exist in such quantities as in the thyroid. In the organs just mentioned it never forms more than 0·001 per cent., whereas in the thyroid the minimum amount necessary for health is 0·01 per cent., while the maximum quantity of 1·16 per cent. has been recorded by Cameron. He finds also that under normal conditions the diet always contains sufficient iodine for the upkeep of this minimal amount. Nor does any other organ or tissue of the body possess the power to fix iodine in organic combination; this property of thyroid tissue is unique and specific for this tissue alone.

Cameron has found that iodine exists in the thyroid in organic combination with amido-acid groups. It is present in the

proportion of 0·3–0·9 per cent. per gramme of the dried gland. The entire adult gland contains 2–9 mgs.

Not only does the iodine-content vary with age and diet, but it varies with season and sex. Seidell and Fenger have shown that it is at its lowest ebb during the first few months of the year. Female animals have more thyroid tissue and more iodine therein per unit of body weight than males.

The iodine of the thyroid has been regarded by some as an accidental constituent. It has been thought that among the functions of the gland is that of taking up or trapping excess of iodine and storing it. There is no doubt but that the storage of iodine is one of the thyroid's functions, but it is equally certain that its presence is more than accidental since the therapeutic value of thyroid gland preparations varies directly with their iodine-content. Furthermore, as Marine has shown, the thyroid's state of activity is largely dependent upon the iodine available for the elaboration of its secretion; lack of it causing the gland to take on abnormal action. Thus, while it is not in itself the active principle of the gland, it is the most important constituent of this active principle at present known to us.

Various substances have been isolated from the thyroid gland—thyroiodin or iodothyrin (Baumann), iodothyro-globulin (Oswald), thyroprotein (Beebe)—which have been considered by their discoverers to be either the active principle or to contain it in large amount. The activity of these substances, like that of thyroid extract, is dependent in great measure on their iodine-content. Their therapeutic effects may be good in some cases, but they lack something and are not so reliable or constant in their action as the dried glandular substance prepared by some of the leading pharmacists, or the fresh liquor prepared according to the British Pharmacopœia method.

Within the past year Kendall has isolated an organic compound of iodine in crystalline form to which he refers as "α-iodine," and which is thought to exist in the form of di-iodo-di-hydroxy-indol, but of which the true formula does not yet appear to be certain. It contains 60 per cent. of iodine, and is thought by its discoverer to be the true hormone of the gland. He states

that "the entire activity of the thyroid is manifested by the administration of α-iodine, a crystalline compound, alone. There appears to be no other substance in the thyroid secretion which acts directly. This substance, given even in very small amounts, will supplant thyroid activity, relieving the conditions of myxœdema and cretinism, and in excess will produce symptoms simulating exophthalmic goitre. It appears to have no direct action on the pulse rate. The extent to which the pulse rate is affected depends not on the administration of the thyroid (hormone), but on the simultaneous ingestion of food and in particular of amino-acids. This effect may be outlined as follows: After the administration of the compound there is no apparent effect for many hours. There is no increased pulse rate or drop in the blood-pressure. However, if thyroid hormone and amino-acids are injected simultaneously, the pulse rate is enormously affected, and even death may result, due to the apparently great increase in metabolism going on in the animal. It appears very probable that the thyroid hormone manifests its activity in some way with amino-acids." [1]

There is some ground for the belief that the thyroid secretion may be polyvalent, with special affinities for certain organs and tissues. Thus specific ferments have been obtained from it by the use of Abderhalden's method (Bauer), while Beebe [2] and his co-workers, and more recently Rogers,[3] have lately isolated from it a substance which reduces blood-pressure on intravenous injection, but which possesses, apparently, none of the other therapeutic characteristics of the thyroid extract. These characteristics the residue retains after the removal of the above substance, and it has been employed in the treatment of myxœdema with highly satisfactory results.

Thus the problem of the composition of the thyroid's secretion is very complex; but it is one which in the light of Beebe's, Rogers's and Kendall's researches would appear to be on the

[1] Kendall, E. C., *Boston Med. and Surg. Journal*, clxxv, Oct. 19, 1916. No. 16.

[2] Fawsett, Rogers, Rahe and Beebe, *Am. Journ. Phys.*, xxxvi, No. 2, pp. 77–238.

[3] Rogers, J., *N.Y. State Journal of Medicine*, 1916, xvi, 232.

road to solution. As we proceed with our consideration of the thyroid in disease we shall see that the synthesis of its highly complex secretion is affected by various agencies which, to a greater or lesser extent, alter the qualitative and quantitative relations of its components and disturb its functions proportionately.

SECTION 4

FUNCTIONS OF THE THYROID APPARATUS

So far as is at present known the functions of the thyroid apparatus are four in number :

(1) It governs the growth of all cells, and sustains their functional activity. (2) It controls calcium metabolism. (3) It is a profound katabolic stimulant facilitating the breaking down of exhausted cells and governing the elimination of the waste products of their disintegration. (4) It exercises a protective anti-toxic and immunizing action, defending the body not only against the toxic products of its own metabolism, but against invasion by disease-producing micro-organisms and injury by their products.

These metabolic and anti-toxic functions it exercises by the discharge into the lymph and blood-stream of a complex secretion which contains its active principles, or hormones. Its anti-toxic function is bound up with—and forms part of—the gland's major function of regulating metabolism. For by its action in maintaining the nutrition of all body cells, and of those of other hormone-producing organs, the liver cells in particular, it regulates the production of protective substances and maintains at a high level the defensive mechanism of the body.

So far as we know its metabolic activities are exhibited in the following ways. It regulates the oxygen intake and the carbon dioxide output. It maintains the constituents of the blood—the red cells, the white cells, the hæmoglobin and salts—at a proper level. It has an important influence in regulating the body temperature. It controls the metabolism of those metallic ions necessary for cellular activity, and of albumins, carbohydrates and salts ; it influences arterial tone and is thus concerned in the regulation of the blood-pressure ; it maintains the activity of the

central and sympathetic nervous systems ; it controls excretion by its physiological diuretic action on the renal epithelium and by its action on the liver cells and excretory organs of the body ; it stimulates in a specific way certain other hormone-producing organs, thus securing and controlling their co-operation in regulating metabolic processes ; in short it maintains the efficiency of all cells and thus speeds up and keeps at a healthy level every bodily function.

The thyroid gland is to the human body what the draught is to the fire ; nay more, its iodine by its chemical interaction with certain unknown constituents of the cells, is the match which kindles it.

The thyroid gland is specifically associated in the exercise of its function with the generative organs, the liver, the pancreas, the adrenals, the pituitary gland and the thymus. Besides maintaining the nutrition of the cells of these organs and of their sympathetic nerves, through their agency it controls bodily growth and metabolism in certain directions. Thus, by stimulating the growth and development of the sex organs the thyroid secures through them the progress of mental and physical growth : witness their suppression in cretinism and juvenile myxœdema. Interacting with the pituitary body it is thought to influence skeletal growth ; the pituitary is considered to compensate in some measure for the thyroid in case of the impaired activity of the latter, since in cachexia thyreopriva and myxœdema the hypophysis may attain to two or three times its normal size. The thyroid stimulates and is stimulated by the adrenals, thus indirectly controlling the blood-pressure and securing the supply to all parts of the body of perfectly oxygenated blood. Interacting with the thymus, through the agency of the lymphocytes of this organ, it is thought to regulate the supply of the excess of phosphorus in organic combination which certain systems, particularly the osseous and nervous, require during development and growth (Sajous). It inhibits the action of the pancreas, which is hyperactive in subthyroidic states, and regulates the storage of glycogen in and its discharge from the liver. Thus

by its interaction with the liver, the pancreas and the adrenals, it regulates carbohydrate metabolism. The profound influence which it exercises over calcium metabolism is exerted through the medium of the gonads, thymus, pituitary and probably other endocrine organs.

The whole question of the thyroid's interaction with other organs, whether by the existence in its secretion of hormones having specific affinities for these organs, or by other means, is however, still but little understood.

As illustrating the remarkable action of the thyroid secretion on growth may be mentioned Carrel's [1] finding that brain and other tissues cultivated in vitro grow several times as fast in the presence of thyroid substance as in its absence. Gudernatsch also has shown that in addition to its power to stimulate growth, it possesses the function of differentiation in the development of the vertebrate organism. Thus, the tadpole, by thyroid feeding, can be brought to the point of metamorphosis within eighteen days after hatching, while normally it would require ten or twelve weeks to reach such a stage. Quite recently Marine and Ragoff have utilized this phenomenon as a biological test for thyroid hormone (Tadpole test),[2] and have tested the efficacy of certain thyroid preparations thereby and the effect of the administration of iodine on the hormone content of the gland.

[1] *Jour. Expt. Med.*, 1913, xvii, p. 14.
[2] *Jour. Pharm. and Exp. Ther.* (Balt), 1916, ix, 1.

SECTION 5

THE FUNCTIONS OF THE PARATHYROID GLANDS

These glands I regard as forming an integral part of the thyroid apparatus although differentiated to some extent in their function from the thyroid. The majority of observers, however, attribute to them specific functions which they exercise quite apart from the thyroid. It is necessary, therefore, to state that their disease or ablation is considered to result in "tetany," either through their failure to neutralize or destroy toxic substances, such as amino-bodies, ammonium carbonate (Kendall), or guanidin, which by their irritation of the central nervous system are considered to cause the symptom-complex of tetany; or, through their failure to conserve the calcium-content of the body, thereby causing increased irritability of the nervous system (MacCallum).

It is certain that the performance of these functions is part of the duty of the thyroid apparatus as a whole, but whether their performance is the specific duty of the parathyroid alone is, in my opinion, still in doubt. For surgical purposes it is well to credit them with this duty so that their unnecessary removal in thyroidectomy operations may be avoided.

The whole subject of the experimental removal in animals of part or the whole of the thyroid apparatus, on which conclusions as to the functions of its component parts are based, is surrounded by the utmost confusion. Apart altogether, as Vincent has pointed out, from the anatomical variations in number and position of the parathyroids which renders the complete removal of all parathyroid tissue uncertain and in many cases impossible—as, where parathyroid tissue is included in the thyroid and thymus—it is a surgical impossibility to remove the parathyroids in some animals without at the same time causing grave injury to the thyroid. Thus in rabbits the parathyroids

are usually embedded in the thyroid, yet accounts of their removal and of the resultant symptoms are frequent in the literature. Certainly, in rats the removal of the parathyroids without injury to the thyroid is an utter impossibility (figs. 3 and 65); yet Erdheim describes the symptoms which follow their removal in these animals.

Furthermore, as Monypenny has shown, complete removal of all parathyroid tissue is not necessarily fatal nor is parathyroidectomy alone more rapidly fatal than thyro-parathyroidectomy.

The similarity of the intervesicular tissue of the thyroid to the epithelial cells of the parathyroid, the fact that on complete removal of the thyroid vesicle formation occurs in the parathyroids with the production of a substance having the staining and microscopical characters of colloid (Vincent and Thompson), the fact that thyroid substance is more effective in the treatment of post-operative tetany than is parathyroid substance alone, the fact that in experimentally-produced parathyroid disease the thyroid is also diseased to a greater or lesser degree, all indicate the close anatomical and physiological relationship which exists between the thyroid and parathyroid glands. But that the parathyroids are capable to some extent of functionally replacing the thyroid and that colloid formation in these organs is an evidence of their hyperactivity is, in my opinion, not proven.

Observers of the results of such operative procedures lose sight of the important fact, which indeed may be predominant, that few, if any, laboratory animals which spend their lives in cages are altogether healthy. They are commonly the hosts of intestinal parasites, or their bodies contain micro-organisms which take on pathogenic action as the result of the operation, or whose toxic products act unrestrainedly in consequence of it. Is it not likely that the symptoms which manifest themselves as a result of such operations will vary with the nature of the specific toxins which predominate at the time of the operation or subsequent to it? Indeed, as we shall see, experiment has shown that it is the products of organisms of intestinal origin, for example, which destroy the parathyroids and directly or indirectly lead to irritation of the nervous system and the

production of tetany. Katabolic toxins, on the other hand, exert their deleterious influence by depressing the functions of all tissue cells and causing the myxœdematous symptoms typical of thyroid defect. It seems to me to be the nature of the specific toxins which happen to be present in cases of thyro-parathyroid deficiency that is of practical importance in determining the onset of symptoms as much as the part of the apparatus which happens to be defective. What we need to know are the symptoms and chemical disturbances of nutrition produced by the toxic products of bacterial growth, especially of bacterial growth in the bowel, just as we know the symptoms produced by metallic and other poisons, so that we can recognize them as readily as we would those of familiar poisons. Until we possess this knowledge we cannot attribute the symptoms following on such ablation operations to their proper cause, nor can we affirm with certainty that this or that part of the thyroid apparatus performs this or that function. Failing such information we must be content with the knowledge that in all conditions of thyro-parathyroid defect two classes of poisons are at work: those resulting from impaired metabolism and those resulting from bacterial action either in the bowel or other parts of the body, or both. The symptoms produced thereby depend not only upon the extent to which whole or part of the thyroid apparatus is injured, but also upon the specific action of the predominant toxins.

The parathyroid glands contribute to the anti-toxic function of the thyroid apparatus as a whole, and there is reason to believe that they assist in protecting the central nervous system from the action of certain toxic products of bacterial growth in the alimentary tract. They are concerned also with the regulation of the calcium metabolism. According to Noel Paton and his co-workers the parathyroids exercise a special influence on guanidin and methylguanidin metabolism. They attribute tetany to the accumulation of guanidin in the body consequent on disease or disordered function of the parathyroids.[1]

[1] *Quarterly Journal of Experimental Physiology*, 1917, vol. iv., 3 and 4.

SECTION 6

THE LIFE HISTORY OF THE THYROID APPARATUS

During fœtal life the developing thyroid is peculiarly susceptible to influences which impair the mother's thyroidal resources. It responds to these influences by undergoing hypertrophy or hyperplesia, or succumbs to them by undergoing cell-death and fibrosis. It is the presence or absence of these influences which determine in the fœtus the future capacity of the child's thyroid apparatus. The importance, therefore, of excluding all influences which depress or unduly strain the maternal thyroid must be insisted upon. For this reason also it is of the greatest importance to inquire into the ante-natal history of all backward children and to examine the mother for thyroid defect. If such defect exist, or if there is reason to suppose that it existed during pregnancy, its existence also in the child is likely to be found in greater or lesser degree.

The thyroid apparatus of the fœtus and of young infants contains little or no iodine. At this period of life the thyroid is more cellular, the vesicles smaller and fewer, containing less colloid than in later years. It does not appear that nature intends the organ to attain to full functional perfection until some months after birth. Certainly it is not called upon to exercise its full functional powers during the earlier months of life. This is due to the fact that the maternal thyroid continues in a state of heightened functional activity throughout the earlier months of lactation, during which time the infant derives from its mother's milk part at least of the thyroid secretion which it needs. Cow's milk does not provide this thyroidal element in the same degree or kind; the calf, which is able to fend for itself shortly after birth, is provided by Nature with a thyroid which is functionally more active at birth than is that of the child, and which contains iodine

in an amount relatively comparable to that of the adult animal (Fenger). Consequently it is not dependent, to the same extent, for thyroidal substance on the mother's milk. Hence it is that no form of infant feeding can fully replace the mother's milk; there are few considerations, therefore, which should deter the mother from fulfilling her duty to her child. It must be remembered, however, that sub-thyroidism in the nursing mother may retard infantile development.

With the cessation of suckling, and with the commencement of taking more solid food, the thyroid apparatus of the child begins to act for itself, elaborating its secretion from the raw materials of the food and responding to every call which is made upon it by the processes of increasing growth and the maturation of the bodily functions.

Throughout child life it is in a state of constant activity which may manifest itself especially under slight toxic provocation in hypertrophy of the organ about the period of the second dentition. At puberty also, and with the onset of menstruation, the physiological capacity of the organ is strained to the utmost. At this time hypertrophy is particularly likely to occur. The parathyroids also share in this increased physiological action, their cells showing changes indicative of activity about this period. During menstruation the special function of the apparatus in maintaining the plasticity of the blood and governing calcium metabolism is called upon, since there is great loss of calcium in the menstrual flow. Where it proves incompetent disorders of menstruation occur, disorders which are particularly common in sub-thyroidic girls, and in girls the subjects of Graves' disease.

We have seen that the efficient development of the sex organs, and the stimulus to mental and physical growth which they in their turn provide, is dependent on the thyroid's functional perfection.

The sexual act, and marriage in both sexes increases the gland's activity, and it is liable to swell in consequence, a fact well known to primitive races.

The war has brought to light the interesting fact that married men under forty years of age are on the whole of better physique

than the unmarried—a fact which is probably dependent in considerable measure on the maintenance of thyroidal activity which marriage ensures. Certainly in women there can be no doubt of the benefits which marriage and child-bearing confer—benefits which are due, amongst other causes, to the maintenance of healthy thyroidal activity.

During pregnancy, as has been seen, the parathyroids as well as the thyroid, are in a state of active secretion which is protracted in gradually diminishing degree throughout lactation. The maintenance of this state of activity is necessary for the speeding up of the mammary glands and the continued secretion of milk. Throughout the child-bearing period of life it maintains this high level of activity, reverting between successive pregnancies and lactation periods to the resting state. Generally speaking, therefore, the thyroid is larger, contains more iodine and is more active in the female adult than in the male. Physiological enlargements of the gland are common during pregnancy, while toxic influences of intestinal origin are peculiarly liable to cause goitre at this period. In a recent examination of a large number of pregnant women at the Queen Charlotte Hospital in London, which Dr. Ripmann kindly made at my request, he found that about 50 per cent. showed slight thyroid swellings which had originated during pregnancy. Primiparæ showed such swellings to "a surprising extent." The gland is most likely to enlarge during the fifth and sixth months of pregnancy. Almost identical figures have been reported by Von Graff, who found that of 633 pregnant women who had had no swelling prior to pregnancy, 49 per cent. presented thyroid enlargement.

Conception is to a great extent dependent on an adequate supply of thyroid substance to the organism, witness the fact that pregnancy often follows thyroid feeding in sub-thyroidic married women.

With the onset of the menopause the thyroid function becomes depressed. At this time symptoms of hypothyroidism are apt to appear especially in women who throughout their child-bearing period have been sub-thyroidic. The stimulus of pregnancy to thyroidal activity during this period had sufficed

to mask the gland's defect, which had become apparent on its withdrawal.

Increasing years bring to the thyroid the changes incidental to advancing life, and after the age of forty its arteries become thickened and less elastic, its connective tissue increased in amount. Small cysts may arise in consequence, or calcareous deposits occur in its substance. Its epithelium becomes less active, its colloid—and with it its iodine-content—decreased. In short, the gland undergoes a process of slow atrophy. But with diminishing vital functions the thyroid's work ceases to be of the same importance, and as the fire of life dies down, the stimulating draught of the thyroid becomes more gentle.

Other factors, in addition to those of age, sex, puberty, menstruation, sexual activity and pregnancy, which influence the thyroid's functional activity in health, are season, place of residence and diet. The iodine-content of the thyroid of all animals so far investigated varies with the season of the year; it may be presumed that it does so also in man. The gland's activity varies with its iodine-content; this is at its lowest ebb during the first four months of the year, when the thyroid is in a state of most active secretion. The phosphorus-content also varies at the same time in inverse ratio to the iodine (Seidell and Finger).

The thyroids of a high proportion of healthy animals living at sea-level, or at altitudes 1000 feet above it, are in the "colloid or resting state." But the functional activity of the gland appears to increase with residence at increasing heights above sea-level [17]. This increased action is necessitated by the gland's influence in maintaining the red cells and hæmoglobin at a level appropriate to the altitude. The effect of altitude being to call for a rapid rise in the blood's red cell and hæmoglobin-content, the thyroid responds to this call by increased action. Its increased activity is doubtless also in part due to the diminishing amount of atmospheric iodine with increasing distances from the sea-coast.

As we have seen in a preceding section, diet exercises a marked influence on the functional activity of the thyroid. Thus Watson has shown that in rats fed on an exclusive diet of meat the gland

continues in a state of active secretion with loss of stored-up colloid ; and if the diet is persisted in pathological effects may be produced. These are evidenced by some degree of cell exhaustion, from continued hyperactivity which may lead to symptoms of sub-thyroidism. Hence it is that a mixed diet containing an abundance of vegetable is the natural and most appropriate food for man.

Finally, the thyroid responds by increased physiological action in all mental and emotional states to which the healthy human being is subject—anger, fear, love, grief, anxiety, great mental exertion, as well as in all conditions of physical exertion.

PART II

FACTORS WHICH DETERMINE THE DEPARTURE OF THE THYROID AND PARATHYROID GLANDS FROM HEALTH

SECTION 1

INTRODUCTION

In the preceding sections we have seen that various factors—altitude, season, sex, dentition, puberty, menstruation, the sexual act, marriage, pregnancy and diet—may influence the thyroid apparatus in the direction of increasing its functional activity. All these, however, come within the limits of the gland's normal physiological range of action. It is probable that the slight fulness of the neck to which they occasionally give rise, is due, under normal circumstances, to the increased flow of blood to the gland occasioned by its increased physiological action. In the presence, however, of even slight toxic provocation, and especially where several of these influences exercise a combined action in the same individual, or where there is a congenital lack of functional resource on the part of the gland, the limits of its normal functional range of action may be overstepped and hyperplasia and hypertrophy or, in debilitated persons, atrophy may result. Thyroid enlargements developing under these circumstances, are usually classed as "Physiological goitres," since they are determined largely by physiological causes, but it is well to remember that underlying them all there is, in addition, very likely to be some toxic provocation.

We will now consider what these provocatives of abnormal action are and how they act.

They belong to three great classes: nutritional, infectious and psychic, and include:—

1. Defective or improper food supply.
2. Residence in insanitary surroundings.
3. Bacterial and other toxins.
4. Infectious diseases.

5. Constipation : intestinal stasis ; intestinal toxæmia.
6. Fright, grief, worry and mental distress.
7. Consanguinity and heredity.

These include all those factors which are at present known to influence the thyroid apparatus in the direction of abnormality. A consideration of tumour growth and of malignant disease is outside the scope of the present work.

THE INFLUENCE OF DEFECTIVE AND IMPROPER FOOD-SUPPLY

In 1908 I undertook a series of experiments on goats with the object of conveying goitre from man to these animals by means of fæcally-infected water. It was observed during the course of the experiments that those animals which received a poor diet, and which were ill-nourished, showed a higher percentage of thyroid changes than those which were well fed, all other factors having remained the same in both classes [8, 9, 10].

The influence of mal-nutrition is exemplified also by the fact that the poorer classes suffer more from goitre than do the rich. In certain villages of the Himalayas the conditions of insanitation are alike in both classes, yet the rich suffer less from goitre than the poor, while a certain form of cretinism (nervous cretinism) is almost entirely confined to the lower classes. The same is true of ill-nourished puppies, calves and lambs in certain parts of America (Marine).

Apart from the influence which mal-nutrition exerts on the functional capacity of all bodily cells, the thyroid gland is especially influenced by deficiencies in the food of certain chemical ingredients which are necessary for the efficient elaboration of its secretion and the maintenance of its healthy functional activity. Iodine, as we have seen, is the most important of these substances as yet known to us. Formerly, farmers in America suffered heavily in deaths amongst lambs from cretinism. The addition of iodine to the food of the sheep put a stop to this disease. Its absence from the food gives rise to hyperplasia and hypertrophy and increased activity of the gland, while its presence in sufficient quantity causes the gland to revert to the resting state in which

iodine accumulates in the colloid. The value of any food so far as the thyroid is concerned is, therefore, to a large extent, dependent on its iodine-contents.

Inanition brings about appearances in the thyroid similar to those induced by want of iodine—such, for example, as occur in an exclusive meat diet in which the iodine-content is very low. Under these circumstances the gland's reserve of iodine-containing colloid is soon exhausted, the vesicles are emptied and become smaller in size and shrunken into various shapes; the intervesicular tissue becomes relatively increased in amount—all of

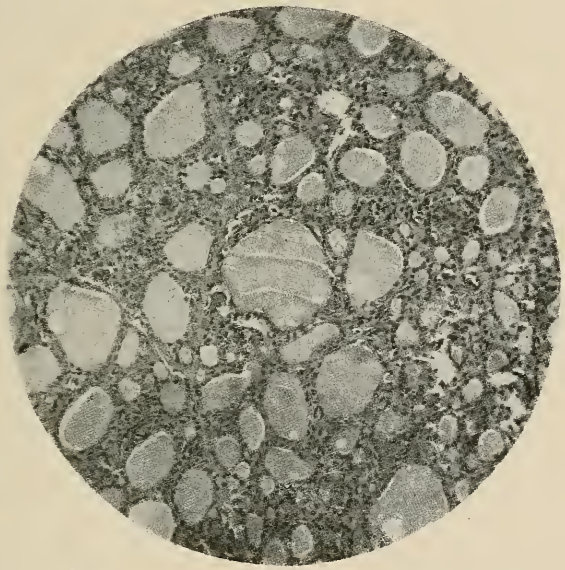


Fig. 5.—Section of thyroid gland of healthy laboratory rabbit. There are some slight evidences of previous hyperplasia in the gland, a frequent finding in animals confined in cages. ×166.

which changes are indicative of an attempt at increased activity on the part of the gland, which is followed by degenerative changes in the parenchyma cells, atrophy, and it may be a diminution in size of the whole organ (figs. 5, 6). The parathyroids are affected by inanition in like manner to the thyroid (Jackson).

Lack of oxygen also produces very similar changes, as is to be expected in the case of an organ whose function it is to regulate the respiratory exchanges. For example, the experimental

stenosis of the trachea in rats, or their confinement in an atmosphere deficient in oxygen, tends at first to increased activity, and later to depression of the thyroid's function.

In the course of hibernation there is a complete disappearance

Fig. 6.—Effects of *inanition* on the thyroid gland of rabbit of same age, weight, and hutch as that of Fig. 5. Note disappearance of colloid, shrinking of vesicles, relative increase of intervesicular tissue; the size of the gland was considerably reduced as compared with controls. ×166.

of the colloid from the vesicles and the gland becomes much reduced in volume (Piser).

That other chemical constituents of the food are no less necessary for the elaboration of the thyroid's secretion than iodine is highly probable. As, however, we are still ignorant of the precise chemical composition of its active principle or principles, we do not know what these substances are.

Conditions which impair the efficient assimilation of the food, and which interfere with the chemical process of the body, will also influence nutrition in such a way as to impair the thyroid. In succeeding sections examples of such conditions will be considered. It is clear that those interfering with the processes of digestion will exert a major effect in this direction. This naturally leads to the conclusion that the essential causes which interfere

with the processes of digestion are amongst the ultimate causes of thyroidal derangement.

A striking illustration of the action on the thyroid gland and on its hormone-producing collaborators of a diet which is deficient in certain ingredients, is afforded by the case of pigeons fed on an exclusive diet of polished rice [21]. The thyroid at first undergoes hyperplasia, loss of colloid occurs from the vesicles, and evidences of cell-exhaustion and desquamation and pronounced atrophy soon make their appearance. The thymus atrophies almost completely, while pronounced atrophic changes take place in the generative organs and the liver undergoes great enlargement.

Pigeons so fed die in large numbers from invasion of the blood by certain micro-organisms of the coli group which may inhabit their own intestines, and which in health, and with a healthy dietary, may exist in this situation as harmless saprophytes. The thyroid changes are due in such cases largely to the septicæmia, and the thymus changes are also due in great part to this cause since they occur on the inoculation of the organism into healthy birds ; but that they are due also in part to the deficiency in diet is shown by their occurrence in cases where the septicæmia has been prevented by isolation of the birds while being fed on the deficient diet.

The effects then of deficiencies of food are not only failure in the synthesis of the thyroid secretion, but a greatly lowered resistance to bacterial invasion. The special antitoxic functions of the thyroid and of its collaborators suggest that these are cause and effect. However this may be, it is important to realize that impaired food assimilation whether due to diet deficiencies or intestinal disorders may result in the body's invasion by its own intestinal saprophytes. Examples of such invasion are afforded in the succeeding section dealing with intestinal toxæmia.

The harmful influence on the thyroid of excessive indulgence in meat diet, as indeed of overfeeding in any form, has already been sufficiently dealt with. It is mentioned again merely to emphasize its importance. Such a diet results in the presence in the bowel of a flora widely different from that found in persons living almost solely on vegetable products.

SECTION 2

RESIDENCE IN INSANITARY SURROUNDINGS

There are few animals which live their lives in cages whose thyroids are wholly normal: there are few fish which live their lives in tanks under artificial conditions whose thyroids are wholly normal: there are few human beings living under modern conditions of life in whom the gland is wholly normal.

In the case of laboratory animals confined in cages, and in birds and beasts in zoological gardens, the widest variations in the histological appearances of the thyroid gland may be seen in animals of the same species. These variations occur in glands of all sizes, from those in which there is hyperplasia without enlargement, and even with diminution in size, to those in which there is actual goitre. Domestic animals also exhibit these wide variations in like degree. Especially is this the case in fowls in which derangements of the thyroid are common, materially affecting their egg-producing capacity. Every successful poultry-farmer realizes the necessity for mixing Epsom salts with his hens' food from time to time, thus combating the intestinal toxæmia from which all animals confined in narrow areas are liable to suffer. The bird-fancier, too, is at pains to prevent his birds infecting their seed and food with their own excrement, which he recognizes as a common source of ill-health. In dogs, living in association with man, thyroid hyperplasia is almost the rule; Marine found this abnormality in as high a proportion of dogs in Cleveland as 90 per cent. In short, it is only amongst fish, birds and animals living in the wild state, and away from the haunts of man and the dregs of his civilization, that wholly normal thyroids are to be found.

This is peculiarly well illustrated in the case of artificially-bred trout. It has been found that in fish confined in tanks

situated one above the other, and from which the water flows from one to the other, the percentage of thyroid hyperplasia and actual goitre formation shows a steady increase from above downwards. Thus fish living free in the stream above the tanks are free from hyperplasia; so are those which live in the stream below the tanks. Moreover it suffices to transfer the fish with hyperplastic thyroids from the tanks to the free life of the stream to cause a complete disappearance of their hyperplasias and even of their goitres. Admixture of the water flowing from one tank to the other with, or its replacement by, pure water also causes a notable decrease in the proportion of hyperplastic thyroids. The extent to which hyperplasia occurs in the thyroids of trout confined in four tanks situated one above the other on the same water-supply is illustrated by the following figures given by Gaylord :—

Water above the tanks	..	..	Fish free from thyroid hyperplasia.		
,, in 1st tank	..	..	,,	3 per cent.	hyperplasia.
,, in 2nd tank	..	..	,,	8 ,,	,,
,, in 3rd tank	..	..	,,	45 ,,	,,
,, in 4th tank	..	..	,,	84 ,,	,,

If iodine is added to the tank water in which these fish live, the hyperplasia is controlled, so also is it controlled by the addition to the water of mercuric chloride in the proportion of one part to 5,000,000 parts of water. The same effect is produced by the addition of arsenic to the tanks in the proportion of one part of arsenic to 300,000 parts of water (Gaylord).

Not only do trout confined in tanks under artificial conditions develop thyroid hyperplasias and actual goitres, but also those living free in streams skirting populated areas.

The significance of these results will be discussed when the question of the etiology of endemic goitre is considered; here they suffice to illustrate the great importance of domestication, especially under conditions of imperfect dietary and insanitation, in giving rise to changes in the thyroid glands of fish, fowl or animal.

Prior to these observations on artificially-bred trout, for which we are indebted to Marine, Lenhart and Gaylord, I

demonstrated similar effects in the thyroid of man due to the increasing impurity of an unprotected water-supply on which certain villages were situated one above the other [1]. It was found that the percentage of goitre showed a gradual increase from the first to the last village on the stream as follows :

1st village	.. ..	11·8 per cent.	goitrous.
2nd ,,	.. ..	18·8 ,,	,,
3rd ,,	.. ..	20·0 ,,	,,
4th ,,	.. ..	26·9 ,,	,,
5th ,,	.. ..	45·6 ,,	,,

These observations have brought to light the important fact that in human beings living under conditions analogous to those of fish in tanks, that is to say, under conditions of imperfect dietary, overcrowding, insanitation and pollution of their food-supply by their own excrement, the same changes occur in their thyroids as in those of trout confined in tanks or animals confined in cages and pens.

In fish, as in animals and man, these conditions affect the thyroid by their action in impairing nutrition, and by their influence in favouring the invasion of the body and especially of the intestine, by micro-organisms of disease.

SECTION 3

THE INFLUENCE OF BACTERIAL AND OTHER TOXINS.[1]

In the preceding section it has been concluded that the increasing prevalence of thyroid hyperplasias amongst the trout confined in tanks was due to the increasing bacterial impurity of the water in the tanks. That the products of bacterial growth have a pronounced action upon the thyroid gland has been proven by the experimental subcutaneous injection into healthy animals of such products in the form of killed cultures in fluid media, and also by the effects on the offspring of animals fed on cultures of certain organisms during pregnancy [16, 24, 19].

These effects are exhibited in varying degrees of hyperplasia, hypertrophy and of cell destruction according to the specific nature and virulence of the poisons, their dosage, the continuous or intermittent nature of their action, and the state of nutrition of the animal.

The organisms whose toxins exert the most marked influence on the thyro-parathyroid glands are those the normal habitat of which is the alimentary tract: *Bacillus coli* and its variants, certain unclassed *anærobes*, *dysenteric bacilli* of all classes, *cholera*, and, according to Farrant, the *B. diphtheriæ*. Toxins absorbed into the system in cases of extensive burns also exercise a pronounced destructive action on the secreting cells of the gland (Valentin).

The effect of bacterial toxins was first noted by Sajous in 1903. I have myself on many occasions observed the pronounced changes

[1] When speaking of the action of "toxins" on the thyroid gland it is well to understand what we mean by the term. It is here intended to include not only the chemical products of the micro-organisms themselves—whether endogenous or exogenous—but also any ultra-microscopic form which they may assume.—R. McC.

which follow the experimental inoculation of such toxins into animals (figs. 7, 8). [19.]

The second factor upon which the action of these posions is dependent is their dosage. Small doses over long periods act as stimulants of the gland's secretory activity. Large single doses of toxic material—as, for example, cobra venom—may produce cell death and desquamation of the vesicular epithelium.

When injections of living cultures are made, very high degrees

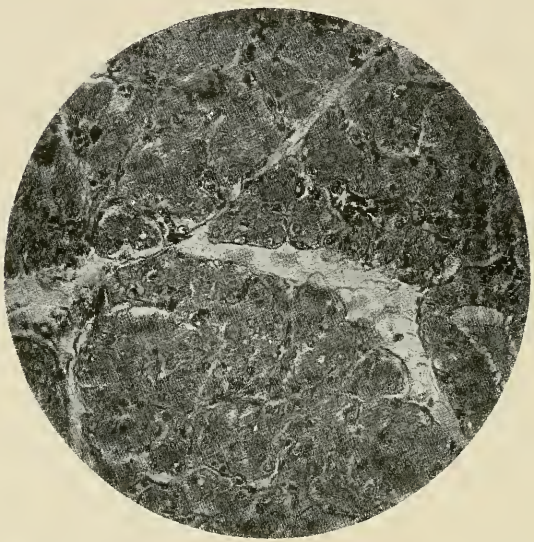


Fig. 7.—Effects of toxic products of *cholera* vibrio on thyroid gland of rabbit. Note capillary congestion, great increase in height of acinar epithelium, almost obliterating acinar cavity, almost complete disappearance of colloid from smaller vesicles and its partial absorption from larger vesicles. Toxin was administered hypodermically. ×300.

of hyperplasia may be observed, hæmorrhages occur into the gland and the destruction of the epithelium is rapid. This is especially notable in the case of *tetanus*, *B. mallei*, and *anthraæ* (Farrant).

Of toxic substances affecting the gland other than the products of bacteria the most important are those produced by helminths in the bowel. Bedson has shown that the mashed-up bodies of these worms when injected into animals in small doses over long periods induce a condition of hyperplasia of the thyroid. In larger doses the hyperplasia eventually gives place to fibrosis, which then

becomes a notable feature of the gland. An even more important observation by Bedson is the fact that such toxic products of worms have a still more pronounced action on the adrenals. The fact that these organs, which are an integral part of the sympathetic system and intimately interact with the thyroid, are stimulated by the toxic derivatives of intestinal parasites, is an etiological observation of high importance.

No better illustration of the action of the toxic products of

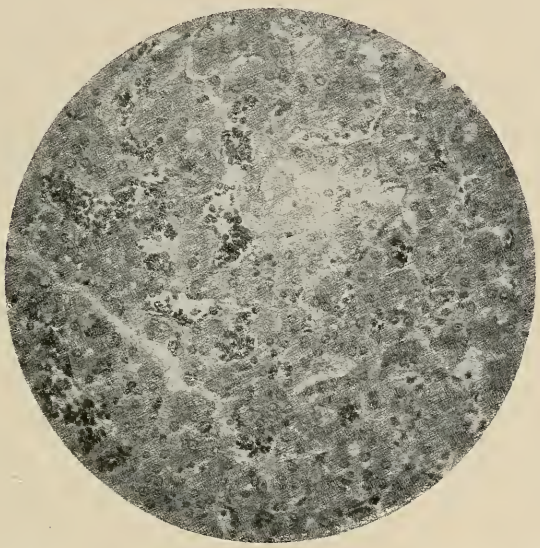


Fig. 8.—Effect of subcutaneous inoculation of toxic products of *Shiga's Bacillus of dysentery.* Note intense congestion, almost complete absence of stainable colloid, great heightening of acinar epithelium. Compare with fig. 10 from an early case of Graves' Disease. ×300.

bacteria could be afforded than that which occurs in experimentally produced congenital goitre, congenital parathyroid disease and cretinism as a result of administering cultures of fæcal organisms to pregnant animals [15]. In this observation the cultures were not killed, but there can be little question that the effects on the fœtal organ were due to the toxins and not to the direct action of the organisms themselves. When so administered these organisms produce effects in inverse proportion to the maternal powers of destroying them. In the majority of cases these powers are so perfect that little or no effect is produced on the fœtal

gland. In cases, however, where the mother's resources are limited the effects are more pronounced. Then the fœtal gland is stimulated to hyperplasia and hypertrophy, while in some cases the process may tend to the total replacement of the parenchyma cells of the fœtal organ by fibroblasts (fig. 25).

Nutritional factors are of great importance in gauging the action of these toxic substances : what may be a minimum dose for a robust individual may be a maximum dose for an ill-nourished one.

SECTION 4

THE INFLUENCE OF INFECTIOUS AND OTHER DISEASES ON THE THYROID APPARATUS

In addition to the evidence of the effects of bacterial and other toxins, afforded by experiments on animals, clinical observations and the pathological studies of Farrant and others have indicated the very great influence which certain infectious diseases and intoxications exert upon the thyroid apparatus.

Among the diseases having a deleterious action upon the thyroid are measles, mumps, whooping-cough, scarlatina, broncho-pneumonia, acute miliary tuberculosis, diphtheria, secondary syphilis, acute tonsillitis, acute rheumatic fever, malaria, trypanosomiasis, helminthiasis, rheumatoid arthritis, pyorrhœa alveolaris and intestinal disorders generally. Less marked in their action are the common cold, influenza, acute anterior poliomyelitis, chronic tuberculosis, gout, lead-poisoning and chronic alcoholism. Those having a rare but severe action are typhoid fever, cholera, the dysenteries, general septicæmia, puerperal fever, erysipelas and orchitis; while rickets, lymphatism and chlorosis are practically always associated with anatomical changes in the thyroid, but as results of these changes rather than their causes.

In the course of these maladies, more especially in the early stages of syphilis, tonsillitis, acute articular rheumatism, general septicæmia, puerperal fever, influenza, typhoid fever, diphtheria, erysipelas and orchitis, sub-acute or acute inflammation of the gland—acute thyroiditis—may occur. This is, however, comparatively rare except in the case of secondary syphilis and acute articular rheumatism, when sub-acute inflammation is common. Indeed a tender thyroid is regarded in France as an important diagnostic point in these maladies. When inflammation does occur, suppuration is likely to result and a degree of thyroid

impairment is produced proportionate to the extent of the resultant cell destruction and fibrosis.

Small encapsuled and benign or torpid abscesses may occur in rare cases after typhoid fever in the subjects of goitre. Melchoir and Gati report several such which were found at operations for the removal of the goitre and were shown to contain typhoid bacilli.

These diseases may also give rise to chronic inflammatory processes which are undetected during the height of the malady, and only make themselves evident by producing thyroid insufficiency after the patient has recovered from the disease. This result is most common in the infectious diseases of childhood, to the deleterious effects of which many cases of thyroid inadequacy occurring in children are to be attributed. It is also to such chronic inflammation of the thyroid in adults that hypothyroidism in all its grades is commonly due.

It is well known that a proportion of patients who have recovered from typhoid fever may increase greatly in weight; this is largely due to the impairment of the thyroid's function which may result from this disease and give rise to a mild myxœdema.

A third mode of action of these diseases is exhibited by the effects which toxins produced in their course may have upon the thyroid gland. This action is especially likely to be exerted in the course of intestinal disorders generally.

Chronic debilitating diseases exert a harmful influence on the thyroid partly owing to their impairment of nutrition and partly to the toxic action of the products of their causal agents. This combined action results in a depreciation of the thyroid's reserve store of physiological energy. Its power of response to stimuli becomes impaired as does its capacity to synthetize its secretion; consequently it undergoes atrophy rather than hypertrophy and sub-thyroidic states are constantly to be met with in those who are the subjects of chronic debilitating diseases. Such diseases are chronic tuberculosis, gout, lead poisoning, chronic alcoholism and intestinal stasis; the influence of the last will be considered in further detail in a succeeding section.

It is believed that certain maladies induce a predisposition to Graves' Disease, or that this condition may actually arise as a thyroiditis produced during their course. Such diseases are: acute tonsillitis, acute rheumatic fever, secondary syphilis and tuberculosis (Levi).

The ingestion of toxic material from the tonsils, the gums—as in pyorrhœa alveolaris—or the naso-pharynx is a common source of thyroidal excitation.

Tubercular processes rarely attack the thyroid and then usually in the course of acute miliary tuberculosis, when miliary tubercles may be found lying between the follicles (Fränkel). But chronic tuberculosis may lead to a degree of thyroid instability and impoverishment which may be an important factor in its functional derangement and predispose to Graves' Disease (Stanton).[1] Tuberculosis again may lead to actual fibrotic induration of the thyroid, as has been pointed out by Roger and Garnier.[2] Bialokur has found symptoms of exophthalmic goitre in 10 per cent. of his tuberculous patients; while Schinzinger has observed such symptoms in 36 per cent. of his cases. Nodular tuberculosis of the gland is rare; it may be of rapid growth and be mistaken for malignant disease.

According to Engel-Reimers swelling of the thyroid occurs in 50 per cent. of early cases of secondary syphilis. He states that it is more common in females than in males, the proportion being 56 of the former to 45 of the latter. Late secondary and tertiary manifestations of syphilis are rare. Syphilitic disease of the gland may occur in connection with the visceral syphilis of infants (Ochsner). Hereditary syphilis or syphilitic taint may be a cause of congenital hypothyroidism (Karcznski), or of Graves' Disease (Clark).

A peculiar form of parasitic thyroiditis (Chagas' Disease)[3] due to the *Schizo-trypanum cruzi* is endemic in Brazil and is said to be spread by the *Conorrhinus megistus*. Its description is, however, beyond the scope of the present work.

[1] *Amer. Med.*, 1915, x, 605.

[2] *Arch. gén. de Med.*, 1900, vol. clxxxv, N.S., iii, p. 385.

[3] For brief account of this malady see the author's Milroy Lectures on Endemic Goitre for the year 1913.

The association of rheumatoid arthritis with endemic goitre is a very common one in goitrous localities of the Himalayas; so much so indeed as to suggest a similarity of origin. This supposition is borne out by the work of Mutch, who has shown to what degree some forms of rheumatoid arthritis are dependent upon staphylococcic infection from the bowel in cases of intestinal stasis. He suggests that ingested staphylococci or other pyogenic cocci sometimes escape destruction in the stomach, and, their growth being encouraged by intestinal stasis, they infect the mucous membrane and surrounding tissues and thereby gain entry into the blood-stream producing morbid changes in the joints.

The beneficial effects of staphylococcus vaccine therapy in the treatment of goitre is of great interest in this connection; for while staphylococcus may not be the cause of goitre, yet it favours its development by the deleterious influence of its products on the gland. Thus the action of the specific goitrigenous agent is facilitated and the association of goitre with rheumatoid arthritis is more readily understood.

While it is probable that few thyroids wholly escape injury during the course of these maladies, it must be admitted that permanent impairment of thyroidal function is the exception; restitution of the gland to the normal state of activity is the rule. It is extraordinary, as Marine has pointed out, with what facility the thyroid can be restored to a comparatively normal functional state even after very decided departure therefrom. But the restitution is dependent on the duration of the abnormal process, on the degree of cell death and fibrosis which has occurred, on the age of the patient, and on his state of general nutrition. The thyroids of well-nourished children, for example, will recover more quickly and more completely than those of ill-nourished children. In adults, in whom the processes of senile atrophy may already have set in, the thyroid is very liable to be impaired permanently by attacks of infectious disease. In the young such parts of the thyroid as have escaped permanent impairment are capable of compensating to a great extent for the injury which the gland as a whole may have sustained; in older subjects

this power is gradually lost. Hence it is that thyroidal defects in children should be detected as early as possible, so that the impaired thyroid may be afforded the specific assistance of thyroid extract and of proper nourishment in its attempts at restitution and compensation.

Infectious diseases, then, may influence the thyroid apparatus—

1. By causing acute inflammation of the gland during their course (comparatively rare).
2. By causing chronic inflammatory processes (more common).
3. By the action of their toxins on the gland (common).
4. And by their interference with the normal processes of nutrition (common).

SECTION 5

THE INFLUENCE OF INTESTINAL TOXÆMIA

This brings us to a consideration of intestinal toxæmia as a cause of thyroid abnormality.

Throughout the previous sections it has been impossible to escape more or less casual reference to this the most important of all influences affecting the thyroid.

In the year 1906 I demonstrated, by my successful application of intestinal antiseptics to the treatment of simple goitre, the important influence which toxic absorption from the bowel exercised upon the thyroid gland. The use of the antiseptics was suggested to me by the fact that in some of the lower animals the thyroid gland (or the structure representing it) was connected with the upper end of the intestinal tube by a duct, and possibly exercised a destructive action on bacteria entering the tube. Salol was first used, later thymol, and later β-naphthol [2]. Their action will be more fully discussed in the chapter dealing with the treatment of goitre.

The accuracy of this observation was established by my further experimental researches [3, 9], and was confirmed by the observations of Sir Arbuthnot Lane from a wholly different standpoint.[1] He first observed the connection between the intestine and the thyroid in the case of a middle-aged woman, the subject of chronic intestinal stasis, who was at the same time a sufferer from a large goitre. The question arose as to the removal of the goitre prior to the correction of the stasis by surgical means. The woman, however, refused and the operation of short-circuiting was performed. Not only did the general symptoms from which she had previously suffered undergo immediate improvement, but the goitre diminished rapidly and

[1] Chapple, H., *Clin. Journ.*, 1911, xxxviii, p. 102.

very distinctly in size, so that on her discharge from hospital it was less than half its original volume. Sir Arbuthnot Lane, during his operative procedures for the relief of chronic constipation, has on numerous occasions noted similar results, reference to which will be found in his own writings and those of his pupils.

After the restoration of the normal drainage of the bowel in cases of intestinal stasis associated with goitre, the thyroid undergoes a rapid and extraordinary diminution in size which is only equalled by that which occurs in cases successfully treated by intestinal antiseptics or vaccines. In one case which I saw before operation, and was able to follow throughout convalescence, the result of correction of intestinal stasis on the thyroid was most remarkable. A girl, aged twenty, was admitted under the care of Sir Arbuthnot Lane at Guy's Hospital, with symptoms of intestinal stasis accompanied by a uniform enlargement of the thyroid of about one year's duration. She was well nourished, but had the cold hands and feet, the poor complexion and other signs so characteristic of this condition. A "controlling appendix" and ileal band (Lane's first kink) were removed by Sir Arbuthnot Lane through a MacBurney's incision. No other treatment except the use of paraffin was adopted. Within forty-eight hours of the restoration of normal drainage the thyroid began to diminish in size and when I examined her two weeks later the circumference of the neck had fallen by two inches and only slight traces of thyroid enlargement remained. Such a result in such a case is not possible from any other treatment except that by intestinal antiseptics or vaccines.

Since my original observation as to the effect of intestinal antiseptics on simple goitre I have been able to provide further proof of the influence of the toxic products of intestinal organisms. As a result of the oral administration of cultures of fæcal bacteria in broth or agar, goitre, cretinism and parathyroid disease have been experimentally produced in animals or in their offspring [9, 10, 16, 24]. These experiments will be referred to under their appropriate headings and in the Appendix.

In 1911, I obtained from the fæces of a goitrous horse a spore-bearing organism having well-defined characters [10]. This

organism was administered to goats in large quantities daily with the striking result that the thyroid glands of three out of four goats so fed were considerably smaller than normal. In one case the gland was only one-third of the normal weight. Microscopical examination showed that pronounced hyperplastic, atrophic and fibrotic changes had also taken place. In one case they were so marked as to resemble those seen in a case of commencing myxœdema (fig. 9). The animal showed such an increase in weight as to suggest this disease. The diminution in size, associated with atrophic and fibrotic changes in the gland, is of great interest

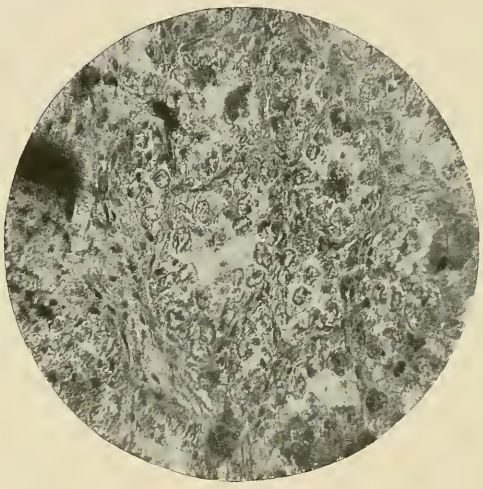


FIG. 9.—Effect on thyroid gland of feeding goat on cultures of intestinal spore-bearing organism. The size of the gland was only one-third that of controls. Note disappearance of colloid, destruction of parenchyma cells, marked disquamation and great increase of fibrous tissue. The great increase in weight of this goat in comparison with controls indicated that this is to be regarded as a case of *Experimentally produced myxœdema.* ×500.

in connection with Sir Arbuthnot Lane's finding that in cases of severe intestinal stasis diminution in the size of the gland is the rule. The toxins of this organism were peculiarly virulent, and gave rise to tetany when administered to dogs. A vaccine prepared from it was successfully employed in the treatment of goitre (figs. 46–48).

The pronounced influence of intestinal bacteria and their toxins on the thyro-parathyroid glands as shown by experiment

on animals, the curative action of intestinal antiseptics in cases of goitre, and the effect on associated goitres, in cases of stasis, of surgical restitution of intestinal drainage, provide incontrovertible proof of the great influence of intestinal toxæmia in producing disordered states of the thyroid apparatus.

Broadly speaking the effects of intestinal toxæmia are manifested as enlargement of the gland or as diminution in its size. The former will follow on the hyperplasia which the toxæmia induces in young well-nourished subjects. Thyroid enlargement will also arise in the presence of an excitant which stimulates the gland but does not kill its secreting cells. Some organisms have a specific action in this way as is the case in those operating to produce endemic goitre. In other subjects, however, as in those who have congenital thyroid incapacity (see Cretinism), in persons over forty in whom the processes of senile atrophy have already commenced, in ill-nourished persons or the subjects of chronic debilitating diseases, or in cases where the virulence of the toxæmia is extreme, the thyroid's powers of continued response to stimuli may be impaired, in which case atrophy and not enlargement will result as in the case of the goats in the preceding experiment (fig. 9).

The experimental production of thyroidal atrophy, of goitre, of congenital goitre, of cretinism, and of parathyroid disease by the administration of cultures of fæcal organisms to animals has enabled us to realize to some extent the deleterious influence of the intestinal flora on the thyroid apparatus. The work of Dr. Nathan Mutch, on the bacteriology of the small bowel in intestinal stasis, carried out in association with Sir Arbuthnot Lane, throws a further light on their possible mode of action. Hitherto we have regarded the large bowel as the source of all intestinal toxæmias, due mainly to the teachings of Metchnikoff, and have failed to attach to the small bowel, the duodenum and stomach any part in their origin. Lane's work has taught us that by the damming up of the intestinal contents in the large bowel stasis may occur in the small bowel, as well as changes in the duodenum and stomach, which render them liable to invasion by micro-organisms either from the mouth above or the large bowel below.

Intestinal stasis is thus a frequent source of infection of the duodenum and small bowel. Infection of these parts of the alimentary tract may, however, occur under other circumstances, one of which is the continued ingestion of bacteria-laden material; as of pus from the mouth or nose or of food contaminated by micro-organisms. These may pass the stomach and become implanted in the duodenum or small bowel, where their presence is abnormal. Mutch [1] has summed up the action of bacteria in abnormal situations in the alimentary tract as follows: "Intestinal bacteria give rise to symptoms of disease by generation of poisonous decomposition products from the chyme and by infection through the intestinal mucosa, with the discharge of bacterial toxins into the circulation. The upper portions of the intestinal tube are laden with food products useful alike for human and bacterial life, and the presence of many organisms in these parts results not only in much waste, but in the formation of highly poisonous modifications of our food materials such as amines and ptomaines. On the other hand, although the colon can absorb sugar and proteolytic products as well as water and salts, it is normally given small opportunity of exercising this function, since mere traces of diffusible carbohydrate and amino-acids pass the ileo-cæcal valve. The loss of these remnants is inconsiderable, but it is most important that toxic modifications should not be evolved. A luxuriant colonic flora is, therefore, provided to ensure their rapid destruction into relatively innocuous bodies, such as phenol, ammonia, water, carbon dioxide, hydrogen, whilst being stored up in the colon for daily evacuation. To put the matter briefly, the alimentary tract is specialized for aseptic absorption of food and the colon for bacterial destruction of residues. The invasion of the ileum in constipation by a restricted number of bacteria, not too versatile in their chemical potentialities, gives rise to various food decompositions and the nature of the toxins elaborated depends upon the particular combination of organisms present."

It will be realized from this and from what has been said in preceding sections to what an extent such an abnormal process

[1] Lane, *Chronic Intestinal Stasis*, London, 1915.

of digestion will hinder the thyroid in the elaboration of its secretion, apart altogether from the toxic action of its poisonous products on the secreting cells of the gland and on other organs and tissues of the body.

A special interest attaches to some of the organisms found by Mutch in the small bowel (*B. coli* and *staphylococcus*) in view of the action of vaccines prepared from them in the treatment of goitre (figs. 33, 34, 35). Having regard to the fact that their toxins are capable of producing thyroid hyperplasia, it is possible that in certain cases they may be the determinants of toxæmic goitres.

There is another factor in intestinal intoxication which must not be overlooked, namely, the migration into the blood-stream and organs of bacteria or other organisms from the alimentary canal and the action of these on the thyroid gland. We have seen with what facility this migration may occur in conditions of mal-nutrition. It is not surprising, therefore, to find that Rosenow has grown from a number of thyroids removed at operation in Graves' Disease, a strepto-bacillus of definite characters. This organism is, however, not necessarily the causal agent of the disease. The possibility having occurred to me that spirochætes might be found in the thyroid in certain cases of simple goitre, I have, with Thompson, examined the juice of such goitres by the dark-ground method immediately after removal from the body but with negative results. Kolle records similar negative findings. Cultural methods of examination of simple goitres have also yielded negative results, so that such goitres cannot be attributed to the presence in the gland of micro-organisms.

Sufficient has been said to indicate the very great importance of all abnormal states of the alimentary tract in influencing the departure of the thyro-parathyroid glands from normal. They act (1) by interfering with the normal synthesis of the thyroid's secretion; and (2) by the direct action of toxic substances produced in their course in causing states of chronic toxic inflammation in the gland. They permit also of the invasion of the blood and tissues by intestinal bacteria, and facilitate the growth and development in the alimentary tract of organisms whose action on the thyroid is specific.

SECTION 6

CONSANGUINITY AND HEREDITY

The influence of consanguinous unions on the thyroid is of great importance. Amongst the Syeds of Gilgit cretinism is much more common than amongst other members of the community. The Syeds of all Mohammedan countries, as descendants of the Prophet, are permitted to marry only in their own sect. In Gilgit these Syed families are few, and it is practically impossible for one of their members to marry out of a goitrous family. As a consequence the stock is goitre-tainted and the taint is accentuated by in-breeding.

Heredity is a factor of importance in the development of all states of thyroid derangement, although it is difficult to estimate the extent of its influence. There is, however, no more constant feature in the history of sub-thyroidic persons than that of sub-thyroidic family history. The operation through generations of influences which tend ultimately to depression of the thyroid function leads to the evolution of a type of thyroidal cell of low functional resource. This congenital debility of the thyroid is a factor of the first importance in the genesis of its disorders.

SECTION 7

PSYCHIC INFLUENCES

Fright, anxiety and mental distress are factors which have a great influence on the thyroid apparatus. All these mental states are to be regarded as expressions of fear. How they may act is well expressed in the words of Crile: "Under the influence of fear, most, perhaps all, of the organs of the body are divided sharply into two classes. First, those that are stimulated, and those that are inhibited. Those that are stimulated are the entire muscular system, the vasomotor and locomotor system, the senses of perception, the respiration, the mechanism for the erection of the hair, the sweat glands, the thyroid gland, the adrenal gland (Cannon), and the special senses. On the other hand, all the digestive and procreative functions are inhibited. What is the significance of this stimulation of some and inhibition of other organs? As far as we know the stimulated organs increase the efficiency of the animal for fight or for flight." When, as in the human subject under modern conditions of life, neither fight nor flight is *de rigueur*, the individual "under the stimulus of fear may be likened to an automobile with the clutch thrown out but whose engine is racing at full speed. The gasoline is being consumed, the machinery is being worn, but the machine as a whole does not move, though the powers of its engine may cause it to tremble." The simile may be carried further and the thyroid's part likened to that of the carburettor whose function it is to regulate the consumption of fuel.

But the factor of fear may influence the thyroid not only directly but indirectly through the adrenals, with which it is known to be intimately associated in its activities, the one stimulating the other. It calls into play what has been described by Cannon as the "emergency function" of the adrenals, and

through the splanchnic nerves causes adrenalin to be poured into the blood in large amount. Under these circumstances there may be produced the staring eye, the frightened facies, the greatly increased supply of blood to the heart, the lungs, the brain and the muscles, the heightened activity of the thyroid, and general excitability of the sympathetic system, all of which are characteristic features of Graves' Disease, which malady indeed has been likened to " continuous fear."

Thus the stimulus of fear in whatever way or form it may act—as fright, as constant worry, anxiety or grief,—may impose an added strain on the resources of the thyroid apparatus, which may be a determining factor in its hyperplasia and hypertrophy, and in its continued hyperactivity and consequent atrophy.

Neurasthenia, conditions of mental and nervous fatigue and overwork may be included in this category, while the shock of trauma or accidents will be found to be a frequent factor in lighting up latent thyroid instability and in precipitating the onset of thyroidal disorder.

We have seen from the preceding sections that the factors which are responsible for the genesis of thyroidal disorders are of three great classes : nutritional, infectious and psychic. All of these may act together in the same individual, the influence of one favouring the action of the other. Especially is this the case with nutritional and microbic factors, the nutritional favouring the action of the microbic, or the microbic, by producing disordered states of digestion, assimilation or absorption, inducing disturbances of nutrition.

It will be realized from the foregoing account of the factors which induce abnormalities of the thyro-parathyroid glands to what an extent all these factors are favoured in their action by the conditions of modern life, with its stress and strain, its poverty and its excesses. A knowledge of the deleterious effects of these factors will enable us to look with an altogether wider vision on many of the cases of thyroidal disorder which come before us.

SECTION 8

PATHOLOGY

Excluding inflammations, the histological evidences of the thyroid gland's departure from normal are in all cases the same in their beginnings. They are modified only in degree by the age and state of nutrition of the patient and by the specific nature, virulence, dosage and continuity of action of the exciting agents at work. In all cases a state of "active secretion" is initiated which gradually merges into one of "abnormally active secretion." The point of departure from normal is difficult to determine, but there are certain signs which indicate it with more or less distinctness. These are :—

1. An increase in height of the vesicular epithelium beyond low columnar type—high columnar epithelium is never found in the normal gland.
2. An increase in number of the vesicular and parenchyma cells.
3. The formation of new vesicles.

The first stage in the process of departure from normal is, therefore, an exaggeration of the normal process of active secretion :

1. The vessels become more engorged and tortuous, the peri-vesicular capillaries more distended. The more acute the process the more marked the congestion. Actual hæmorrhage may occur in consequence of the hyperdistension of the capillaries, and red cells not infrequently escape into the acini (fig. 10). The lymph drainage is increased ; the veins are engorged. The gland becomes larger, of a bright red colour, and is softer to the touch.

2. Absorption of the stored-up colloid occurs, and it soon wholly disappears from the hyperactive organ.

3. An increase in the height and number of the cells lining the acini occurs (figs. 10, 11, 12). The cells become high columnar. The protoplasm of the hypertrophied cells is more conspicuously reticulated, and may contain clear spaces, especially in the neighbourhood of the nucleus (figs. 11, 12, 13).

Desquamation of the vesicular epithelium may occur, part or the whole of the cell being discharged into the acinar cavity.

A characteristic feature of the cells at this stage, and one in which it is in marked contrast to the normally secreting cells, is

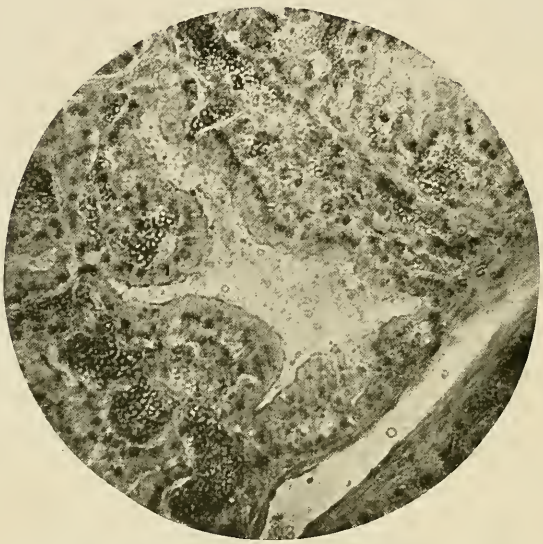


Fig. 10.—Section of thyroid gland from early case of Graves' Disease, showing great congestion of capillaries, high columnar epithelium lining the irregularly shaped vesicle, absence of stainable colloid, and blood corpuscles and cellular debris in vesicle. From a specimen in the possession of the late Sir Victor Horsley, F.R.S.

the striking variation in size, shape and staining characters of the parenchyma nuclei. Some are much enlarged, and may be either deeply stained, hyper-chromatic or vesicular; these nuclei are oval or spherical in outline, and may measure 8 to 10 μ in diameter. Others are small, intensely staining or pale-staining; these represent recent-division forms. Others are irregular, kidney-shaped or pyriform. These diverse nuclear appearances are the evidence of abnormal cell-division. Mitotic figures are occasionally met with, especially in young glands. These

changes have been observed in experimentally-produced goitre in rats [19].

4. The cellular increase gives rise to an increased thickness of the acinar walls, to outgrowths of the epithelial lining forming buds and plications of the acinar wall (figs. 10, 13, 14).

5. Thus the vesicles lose the comparative symmetry of their outline and become most irregular in shape (figs. 14, 15, 16). The high columnar lining encroaches on the acinar cavities, and these become relatively smaller.

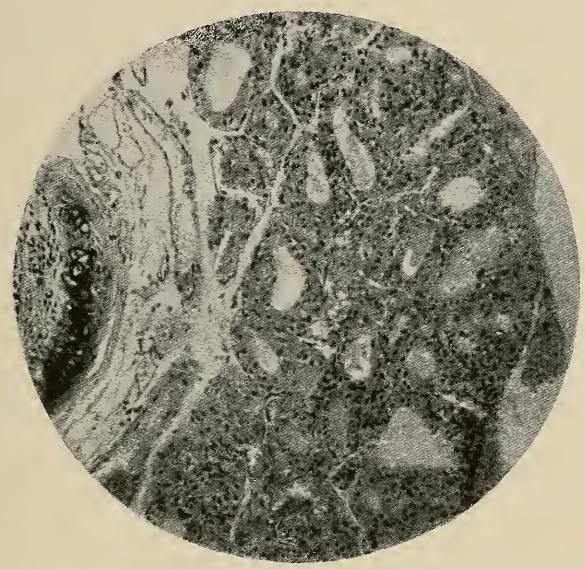


FIG. 11.—Section of thyroid gland showing experimentally-produced goitre in mouse, due to contamination of food with goitrous fæces. Early stage; note absorption of colloid, great increase in height and multiplication of acinar epithelium, increased intervesicular tissue; the vacuolation of the protoplasm of the acinar cells, due to the discharge of secretion, can be made out in some parts of the specimen. × 166.

6. Many new acini are formed in the intervesicular tissue (figs. 12, 13).

7. In artificially-produced goitre in the rat granular masses of intensely staining basophil granules, lying in the intervesicular tissue, are conspicuous objects. They resemble masses of cocci, but are probably the granules of mast cells.

8. There is a greatly increased discharge into the lymph spaces and acini of thin gelatinous secretion from the heightened

epithelium ; it is very pale-staining. The edges of the epithelial cells often merge with the secretion in the acini, or break off to form part of it. The acini contain a *débris* of broken-down cells into which leucocytes and red blood corpuscles wander (fig. 10).

9. *Pari passu* with this multiplication of cells and new vesicle formation, a greater or lesser increase of the fibrous stroma (fig. 16), and an accumulation of lymphoid cells occur ; the latter may form a conspicuous feature of the gland in cases of Graves' Disease, but is not so evident in simple goitre.

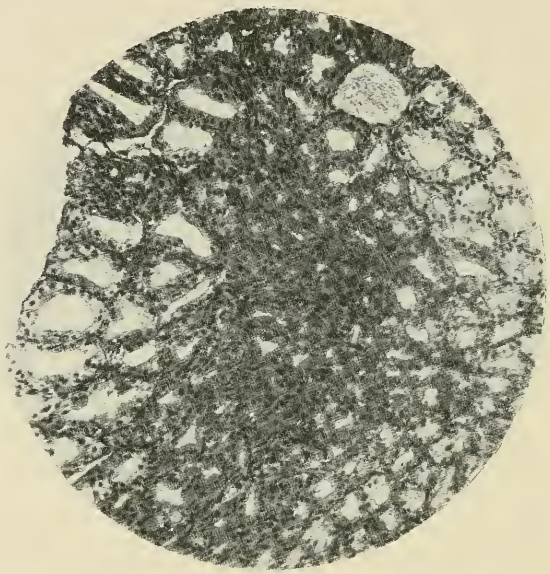


Fig. 12.—Section of goitrous thyroid of rat. Due to feeding on intestinal anaërobes. Note disappearance of colloid ; small size of vesicles, many new ; high vesicular epithelium, vacuolation of protoplasm around nuclei ; great increase of intervesicular parenchyma. × 166.

The process is largely compensatory in character, but to it is added a chronic inflammatory element due to the action of toxic agents on the gland. It may vary in its acuteness or in its chronicity, as well as in degree. The whole organ may be involved in it, and is so as a rule, but occasionally different parts of the gland may be affected in different degrees. It may or may not give rise to enlargement of the gland depending on the virulence of the toxin, the continuance of its action, the state of nutrition

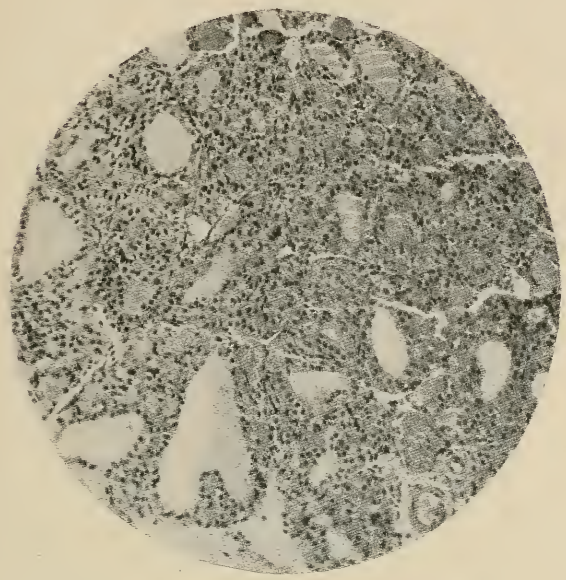


FIG. 13.—Section of goitrous thyroid from a rat fed on cultures from goitrous fæces. Note absorption of colloid, great increase of intervesicular parenchyma, formation of new vesicles of small size, well marked "bud." There is a great increase of fibroblasts in this gland. × 166.

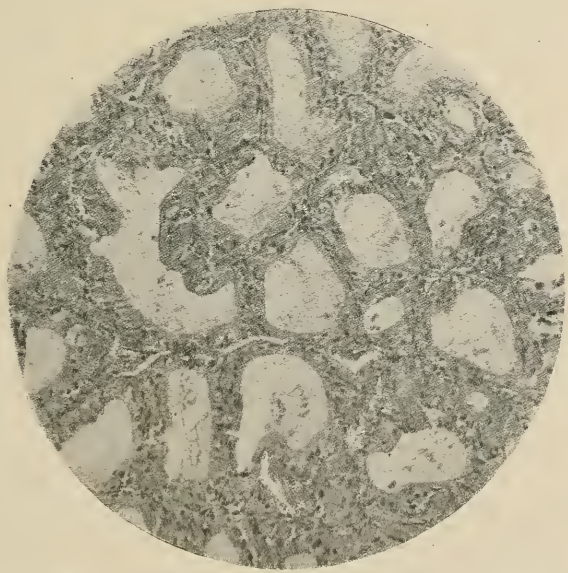


FIG. 14.—Section of goitrous thyroid of rat which suffered from symptoms resembling tetany. Note high columnar epithelium, disappearing colloid, irregular shaped vesicles, the piling up of the epithelium forming "buds." There is also marked capillary congestion which is not well shown in figure. × 166.

of the individual, and the gland's powers of response to toxic or other stimuli. Depending also on these factors it progresses to a definite end. Thus, under certain conditions of malnutrition, such as may occur in severe toxæmias of intestinal origin, or, as a result of infectious diseases, the gland's powers of response are limited in greater or lesser degree, so that after a more or less abortive attempt at the process of hyperplasia, atrophy of the secreting cells occurs and they are replaced by fibroblasts (figs. 9, 51). This result is especially liable to occur in persons

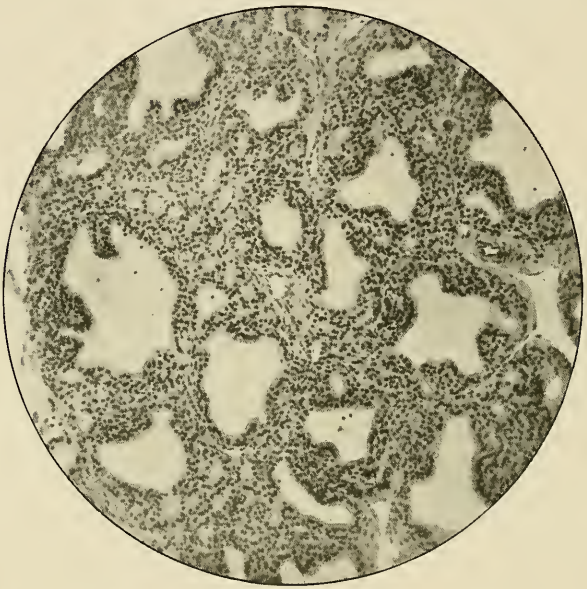


Fig. 15.—Active thyroid hyperplasia of marked degree. Note the irregular size and distortion of follicles, infoldings and plications of the lining epithelium: the regular and uniform, high columnar epithelium; the absence of true colloid and the generalized increase of stroma. (Reproduced by courtesy of Dr. David Marine, Cleveland.)

over the age of forty years, in whom senile atrophy may already have begun. Under these circumstances no swelling of the gland will occur at any stage of the process. In this way cases of *myxœdema* or hypothyroidism may arise in young people as well as in adults, the severity of the resultant symptoms depending on the extent of the cell-death and fibrosis (figs. 23, 24).

In other cases where conditions of malnutrition and thyroid

impoverishment are not paramount, the hyperplastic process takes one of two courses:

1. It reverts to the colloid state, forming the so-called "colloid goitre," or
2. It continues without any period of rest, ultimately terminating in cell-exhaustion and cell-death.

In the first event, the reversion to the colloid type follows that course which has been described as a normal process of

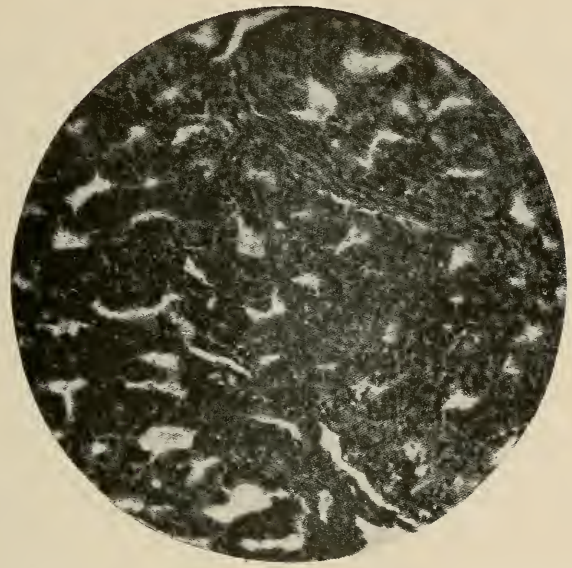


FIG. 16.—Section of goitrous thyroid in rat. Due to the contamination of the animal's food with fæces of goitrous individual. Note high epithelium, irregular acini, absence of colloid, increase of fibrous stroma, marked hyperplasia of parenchyma cells. × 166.

secretion in an earlier part of the work. The old and the new vesicles become distended with colloid, absorption of a number of the new-formed elements occurs, and iodine is again stored in the colloid (figs. 17, 18).[1] The gland reverts to a state which may approach very nearly to normal, but it shows

[1] In goitre produced experimentally in rats by means of fæcal material or by cultures from fæces, the continuous administration of these toxic materials does not permit the gland to revert to the colloid state. Under the conditions of the experiment they are allowed no period of rest, consequently no colloid accumulates in the hyperplastic organ.—R. McC.

the scars of its encounter with the exciting toxins in these ways :—

It is usually increased in size to a greater or lesser extent.

Its capsule is thicker ; its stroma more plentiful.

Its vesicles are more irregular in shape and size, and may show evidences of the previous hyperplasia in the form of sprig-like projections into the interior of the acini, or areas of hyperplasia may be found in the intervesicular tissue (fig. 18).

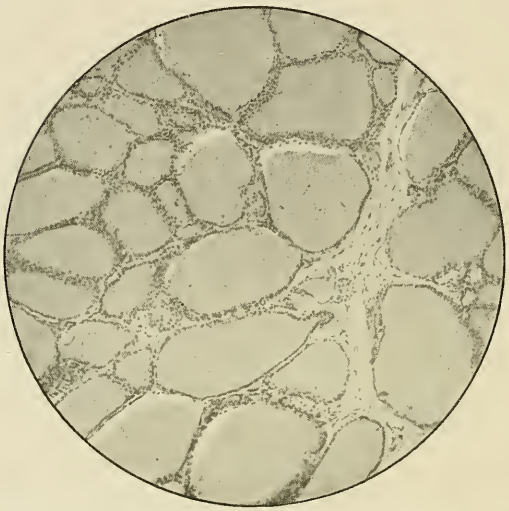


Fig. 17.—Section of normal thyroid gland, in colloid or resting state, from human subject. (Reproduced by the courtesy of Dr. David Marine, of Cleveland). × 50.

Its artery walls are thickened by a process of obliterating endarteritis, or they may even show calcification.

Its veins are lessened in their calibre and the walls of its lymph trunks are thickened.

These appearances will vary with the duration of the hyperplastic stage, and the length of time since reversion to the colloid stage has taken place (fig. 18). Thus the gland may appear more colloid in type and less hyperplastic or *vice versâ*, according to the stage of the process at which it is observed.

This process of reversion to the colloid state, first accurately described by Marine and Lenhart, represents the second stage in

the production of simple as opposed to exophthalmic goitre. Its onset in the case of endemic goitre is determined by the fact that goitrigenous influences are intermittent in their action and, as a rule, are only operative during the spring months in endemic areas.

If, now, a further attack of hyperplasia occurs in such a colloid gland, the whole process is repeated and the scars become more pronounced. In the case of endemic goitre repeated periods of hyperplasia succeed one another during succeeding springs, the

FIG. 18.—Section of colloid goitre from human subject. Note, great irregularity in shape and size of vesicles, their distension with colloid; the evidences of hyperplasia in the form of buds, sprigs and cellular areas; increase of fibrous stroma. × 50.

gland reverting in the intervals to the colloid state. So also in pregnancy successive attacks of hyperplasias may occur with successive pregnancies, periods of rest alternating with periods of activity. A stage is ultimately reached when the secretion finds its way less readily into the lymph channels. The colloid becomes more and more viscid, owing possibly to specific chemical changes, and is dammed up in the vesicles by the increasing stroma.

There may also develop in the gland rounded or circumscribed masses apart from the main body of the goitre (figs. 19, 20).

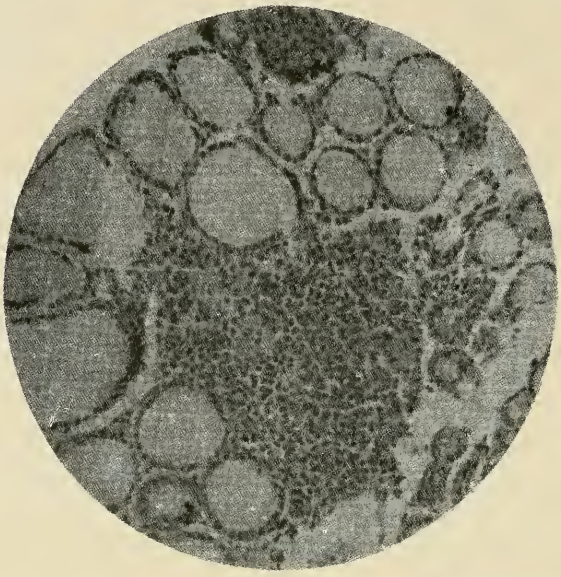


Fig. 19.—Collection of round cells and multiplying parenchyma cells in thyroid of mouse fed on fæcal material. × 200.

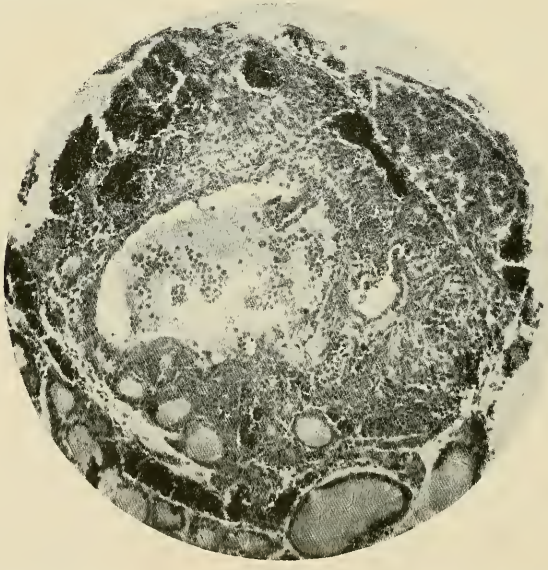


Fig. 20.—Small nodule in mouse's thyroid showing marked congestion at periphery, degeneration of central area. Thought to be a later stage of process shown in fig. 19. From a mouse receiving fæcal material with food. × 100.

These are usually called " simple adenoma," or " fœtal adenoma," according to their histological appearances. They may occur either in the form of a single nodule or of several nodules scattered through the gland, which, in developing, encroach on the surrounding parenchyma causing its atrophy. This adenomatous form of degeneration is one to which all parenchymatous goitres of long standing are peculiarly subject, and to which they sooner or later succumb. It is extremely common in the goitres of elderly subjects and of cretins.

The development of adenomata, of hæmorrhages due to trauma and cysts resulting from them, the progress of fatty, calcareous, amyloid and hyaline degenerations complicate the initial process, and the nodular and degenerated goitres so characteristic of endemic localities are the result.

In all chronic goitres considerable atrophy of the parenchyma cells ultimately occurs, and the functional activity of the gland per unit of space becomes diminished. The functional power of the thyroid as a whole is, however, rarely so impaired as to cause pronounced symptoms of hypothyroidism.

In the second event the hyperplastic process is continued without any period of rest. It goes on so long as the excitant continues to act without intermission. This is what occurs in Graves' Disease (fig. 21), and this is the essential difference between the goitre of Graves' Disease and simple goitre. Since periods of rest are necessary for the gland's recuperation, ultimate exhaustion of the cells occurs when these are not provided. In this case degenerative changes occur in the secreting cells (fig. 22). They become vacuolated, irregular in shape and size, desquamation increases and desquamated cells and cell-débris fill the vesicles (fig. 23). The nuclei become more irregular in shape and size, and cell-regeneration cannot keep pace with cell-destruction. Fibroblasts take the place of the dead parenchyma cells, and the fibrous stroma of the organ becomes greatly increased (fig. 24). The gland's powers of compensation and cell-regeneration have failed, its reserve force is exhausted. This process results in *myxœdema*, which may follow any prolonged toxic excitation of the thyroid; it is a natural sequel of such

excitation in all cases of Graves' Disease that do not recover spontaneously, or in which death does not supervene. In all

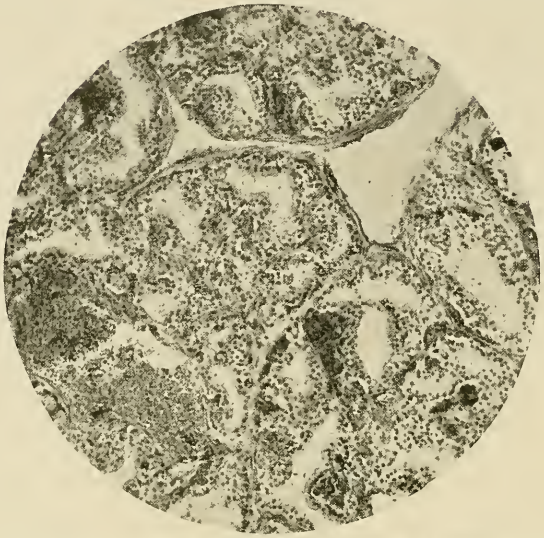


FIG. 21.—Section of thyroid from a case of Graves' Disease. Note heightened and heaped-up epithelium, irregular-shaped vesicles empty of stainable colloid, containing cellular débris; increase of fibrous stroma; also lymphocytic increase. From a specimen in the possession of the late Sir Victor Horsley, F.R.S.

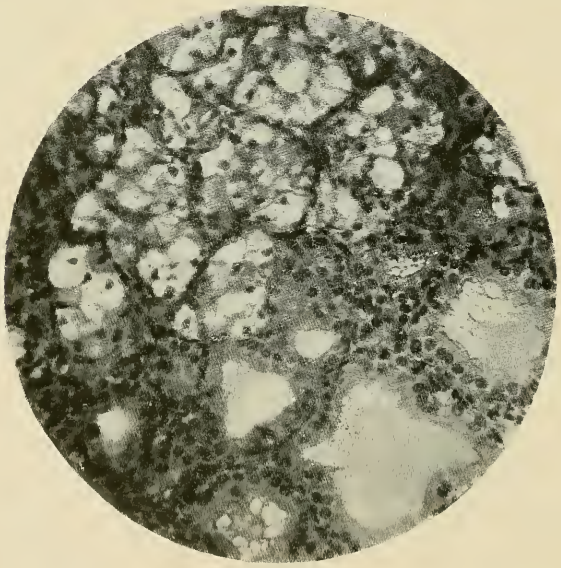


FIG. 22.—Section of goitrous thyroid from rat fed on fæcal filtrate. Note absorption of colloid, columnar epithelium lining acini, commencing cellular degeneration, nuclei lying free and disintegrating, slight increase of fibrous stroma. Represents early stage of parenchyma degeneration. × 350.

cases of this disease which have lasted for a considerable time some degree of thyroid impairment must result.

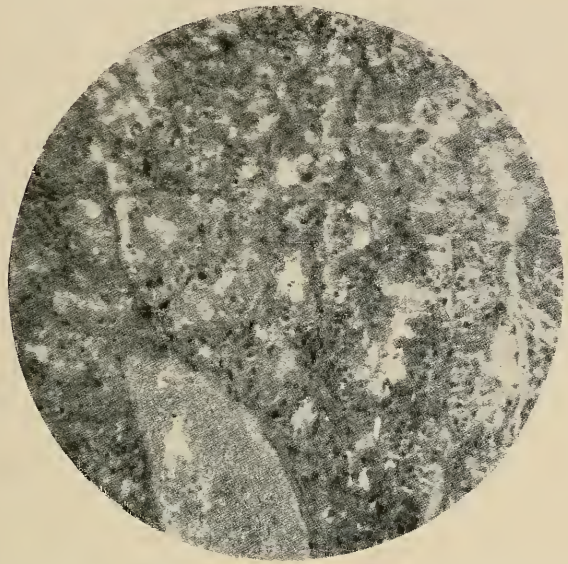


Fig. 23.—A further stage in the degenerative process. Section of thyroid from a goitrous rat fed on fæcal material. Note cellular disintegration, complete absence of acini or colloid, increase of the fibrous stroma. A large distended vessel is also seen. Appearance corresponds to that seen in figs. 9, 24, 51, with which compare. × 200.

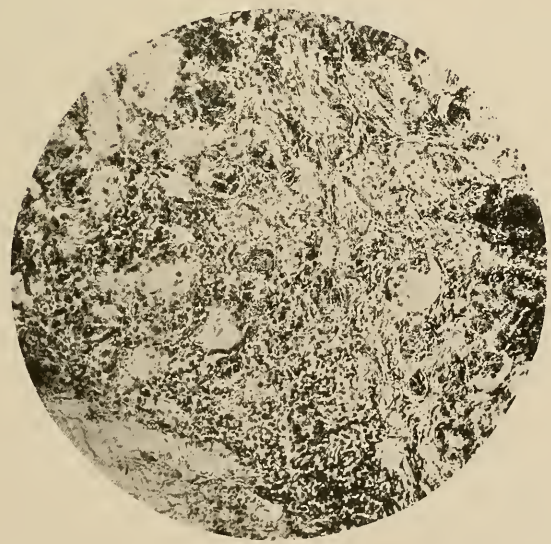


Fig. 24.—Final stage in the degenerative process. Section of thyroid from a case of myxœdema. Note absence of vesicles and colloid, atrophy of parenchyma and great increase of fibrous tissue. From a specimen in the possession of the late Sir Victor Horsley, F.R.S.

It will be recognized that every grade of severity, acuteness or chronicity of this continued excitation-process may occur, as well as every grade of resultant thyroid defect, dependent no doubt upon the nature and dose of the toxic excitant and the coexistence of other influences which excite and ultimately impair thyroidal activity. Ultimate recovery or ultimate cell death will also to a great extent be influenced by the coexistence of the other factors to which reference has been made in the preceding sections.

The changes in the fœtal gland which give rise to *cretinism*, are essentiallly the same as those just described (figs. 25, 64), and are due to toxic agencies acting through the medium of the maternal blood. Their severity is dependent on the nature and dosage of these excitants, and on the state of nutrition of the mother. The process may result in complete fibrosis of the organ (fig. 25), or more commonly in its partial destruction, as in figs. 50 and 67, which show marked fibroblastic invasion of the isthmus, the lateral lobes being but slightly affected.

Throughout the process of hyperplasia, in whatever way induced, certain chemical changes are known to occur in the gland. Its iodine begins to disappear and this disappearance proceeds beyond what is usual for the physiological demands of health. Marine and Lenhart have shown that its disappearance commences just prior to the appearance of the hyperplastic changes and is proportionate to the degree and duration of the hyperplasia. The greater the hyperplasia the less the iodine-content of the gland. The α-iodine in the hyperplastic thyroid of Graves' Disease may be reduced to one-fifteenth to one-eighteenth of its quantity in health (Kendall). We have seen that the factors which give rise to loss of iodine from the gland are its lack in the food, and, much more commonly, disordered assimilation of iodine owing, as I believe, to microbic invasion of the small bowel. The process of thyroid hyperplasia may, therefore, from the bio-chemical point of view, be regarded in some measure as a compensatory one due to the failure of iodine assimilation. Chronic toxic irritation of the gland is the other element in its production.

Marine and Lenhart's prolonged investigations in this direction have led them to conclude that at all stages of the hyperplastic process there is a qualitative deficiency in the secretion, although in its earlier stages it may be increased quantitatively. This quantitative increase of secretion in the blood-stream does not appear to compensate fully for its deficiency in quality, since as the hyperplasia progresses symptoms of thyroid deficiency ultimately

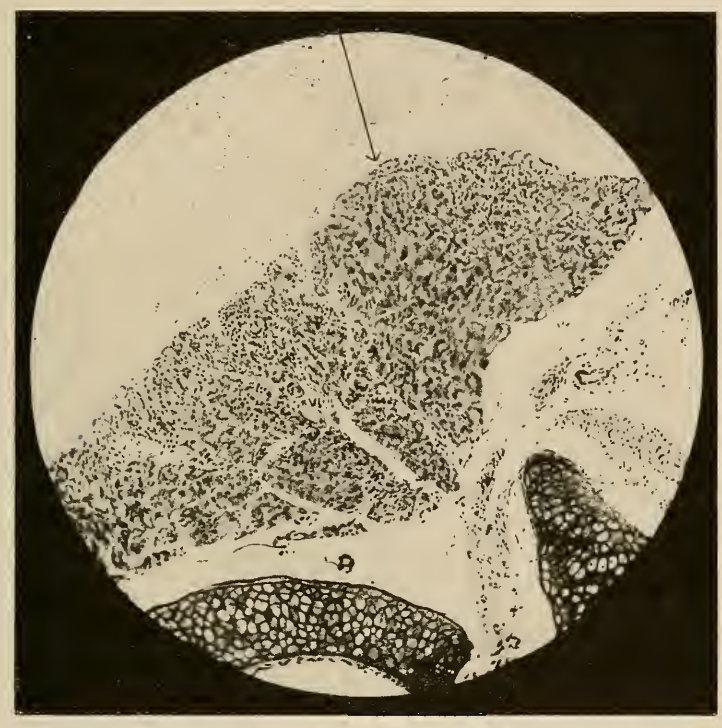


Fig. 25.—Section of thyroid and parathyroid of young rat from a case of experimentally-produced cretinism. The situation of the parathyroid is indicated by an arrow. Both glands are converted into a mass of fibroblasts. × 100.

appear in greater or lesser degree. Thus, in the simple goitre of endemic localities, the functional activity of the organ is impaired per unit of space, although the increase in size may to a great extent compensate for this. In Graves' Disease symptoms of thyroid deficiency appear during its course; and, finally, in myxœdema and cretinism the gland's iodine-content is enormously reduced and its power to elaborate its secretion is impaired in proportion to the degree of cell-death and fibrosis.

These chemical changes deal only with the iodine-content of the gland, which are alone known to us. But it is presumable that others no less important may also occur in consequence of the nutritional, infectious and psychic factors we have discussed, much in the same way as these factors would lead to chemical alterations in the milk secretion.

The question of the chemical alterations of the thyroid's secretion in Graves' Disease will be dealt with when that disease is considered.

The factors which give rise to pathological changes in the parathyroid gland, and the nature of these changes, will be discussed more appropriately in the sections dealing with the congenital manifestations of endemic goitre and with tetany.

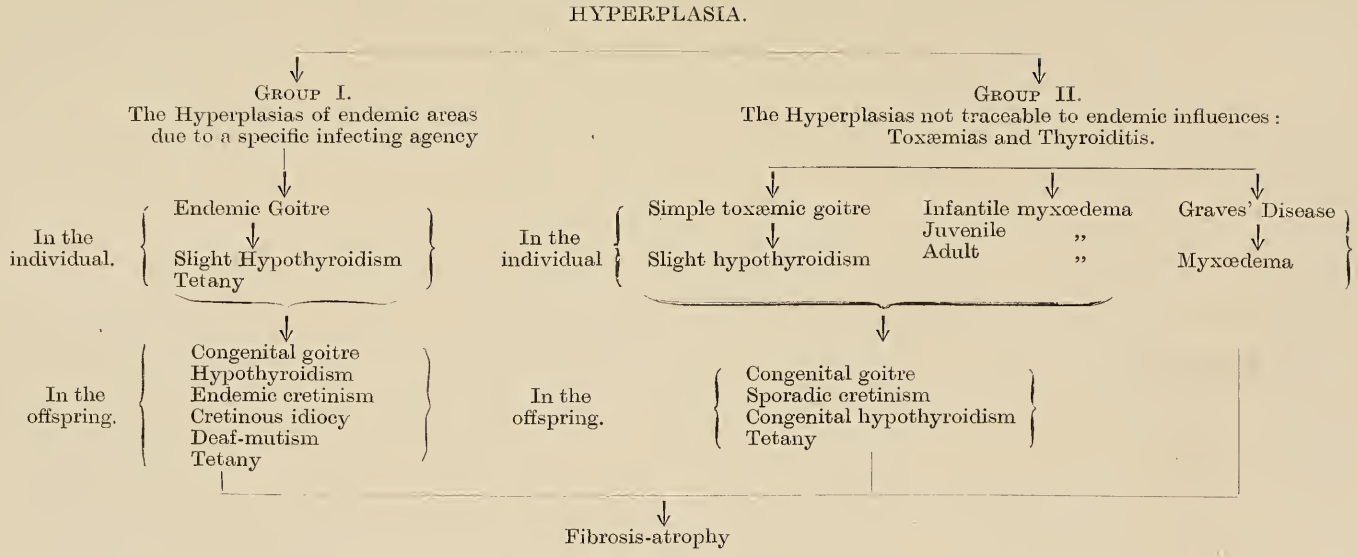
Throughout the second part of this work three main facts connected with the genesis and course of diseases of the thyroid apparatus are brought into prominence.

First: That all these diseases are due to psychic, nutritional, or toxic (including microbic) factors acting either singly or more commonly in combination.

Second: That in all the pathological process is essentially the same—greater or lesser degrees of hyperplasia followed by greater or lesser degrees of fibrosis and atrophy.

Third: That in all there is an alteration in the quantity and quality of the thyroid secretion discharged into the blood-stream.

If for the purposes of classification of these diseases we include the inflammations with the hyperplasias due to infectious diseases, then the diseased states of the thyro-parathyroid glands, with which we have to deal, may be grouped as follows :—


HYPERPLASIA.
Group I.
The Hyperplasias of endemic areas due to a specific infecting agency
Group II.
The Hyperplasias not traceable to endemic influences: Toxæmias and Thyroiditis.
In the individual.
Endemic Goitre
Slight Hypothyroidism
Tetany
In the individual
Simple toxæmic goitre
Slight hypothyroidism
Infantile myxœdema
Juvenile ,,
Adult ,,
Graves' Disease
Myxœdema
In the offspring.
Congenital goitre
Hypothyroidism
Endemic cretinism
Cretinous idiocy
Deaf-mutism
Tetany
In the offspring.
Congenital goitre
Sporadic cretinism
Congenital hypothyroidism
Tetany
Fibrosis-atrophy

PART III

DISEASES OF THE THYRO-PARATHYROID GLANDS

SECTION 1 [1]

ENDEMIC GOITRE

Synonyms.—Struma, wen, Derbyshire neck, Nithsdale neck, bronchocele.

Definition.—A chronic infectious disease occurring in more or less circumscribed areas and characterized by a non-inflammatory and progressive enlargement of the thyroid gland, which is unattended by marked functional disturbances. It is due to the presence in the alimentary tract of certain undetermined organisms, whose toxic products reach the blood-stream and induce in the thyroid gland hypertrophic, hyperplastic and degenerative changes. Acting through the medium of the maternal blood, these toxins may cause hypertrophy and hyperplasia, or fibrosis and atrophy of the fœtal thyroid, thus giving rise to congenital goitre or to the varying degrees of cretinism.

Prevalence.—The extent to which goitre prevails in European countries generally, and in the East, is seldom appreciated. In France, Germany, Austria, Switzerland, and Italy large numbers of conscripts are annually exempted from military service on account of goitre. Baillarger estimated that, about the year 1874, there were in France alone no less than half-a-million goitrous persons and 122,700 cretins and cretinous idiots. In the provinces of Piedmont, Lombardy, and Venice, in the year 1883, one in every 67 of the inhabitants was either goitrous or a cretin. In some Himalayan villages the disease is so common that it is difficult to find a man, woman or child not suffering from the

[1] The major part of this section appeared as a special article in the "Endocrine gland" number of the *Practitioner*, 1915 [23].—R. McC.

deformity. The disease is probably less prevalent nowadays than formerly, but it still gives rise to an immense amount of disability in almost every country in Europe. In India, at the present time not less than five million persons are afflicted with goitre, while half-a-million is a low estimate of the numbers who suffer from its congenital manifestations.

Prevalence in Animals.—In endemic localities, goitre may be met with in domestic animals and birds. It occurs in mules, oxen, horses, dogs, cats, goats, pigs, sheep, white rats, white mice, and in fowls and pigeons. It occurs also in artificially-bred fish, especially in trout, which are often very severely affected. In animals living in the wild state, the disease is infinitely less common, and is generally found only in those whose habits of life have to a considerable extent been modified by the vicinity of man and his domestic animals. Thus, it is excessively rare in wild rats, although under certain conditions of life it may be very prevalent among tame rats.

Although fish of carnivorous habits, such as the pike, are more subject to goitre than are others, such as the carp, their susceptibility to it appears to vary greatly. Certain species of the *Salmonidæ* have an almost complete natural resistance to the disease; amongst susceptible species certain batches reared in captivity show a high degree of immunity (Gaylord).

Congenital goitre commonly occurs in the offspring of goitrous animals (fig. 33), and so-called "epidemics" of goitre amongst domestic animals and artificially-bred fish have frequently been reported. Cretinism also may be found in animals in goitrous localities, as for example, in lambs, amongst which it was at one time very common in Michigan. Amongst animals, as amongst men, those that are well fed and well cared for are much less liable to suffer from the disease.

Geographical Distribution.—Endemic goitre is widely distributed over the whole world. Few countries appear to be entirely free from it. It is so common in certain parts of England and Scotland as to be distinguished by the names, "Derbyshire

neck " and " Nithsdale neck." It is most prevalent in temperate and sub-tropical zones. It is found, however, in regions of great cold, as in parts of Siberia, in Finland, and in the Hudson's Bay Territory of North America. It occurs also in regions of great heat, as in tropical South America, Borneo, Sumatra, Java, India and Ceylon. While, therefore, temperate and sub-tropical climates are more favourable to its development, neither great heat nor great cold excludes its occurrence.

Orographical Distribution.—The association of the endemic with mountainous regions is one of its most striking peculiarities. The Alps, the Pyrenees, the Carpathians, the Himalayas, the Caucasus, the Andes, the Cordilleras, the Ural and Altai Mountains, and, in our own country, the valleys of the Pennine Range, the Cotswolds, and the Mendips, are all noted haunts of goitre. But, while it is true that the disease has its home in the mountain ranges of the world, it is not confined to them. It occurs in the plains of Lombardy, of Piedmont, of Alsace ; in the plains of the Lena and Obi in Russia ; of the St. Lawrence in Canada ; of the Ganges and the Brahmaputra, and of the Chenab and Sutlej in India.

Some mountainous countries, on the other hand, are almost exempt from goitre, as, for example, certain parts of Norway and the Highlands of Scotland, where it appears to be almost unknown. Although the hilly nature of a country cannot be regarded as a necessary factor for the development of goitre, there is considerable experimental ground for the belief that its preference for mountainous regions may, to some extent, be dependent on the increased functional activity of the thyroid gland which residence at high altitudes often entails. [22.]

The unprotected water-supplies of mountainous districts, together with the configuration of the soil, which favours their pollution by surface drainage, are also important factors in favouring the development of goitre amongst the residents in such districts.

The frequent association of goitre with rivers, canals, and irrigated or marshy tracts is another noteworthy feature of its

distribution. [22.] This association is especially obvious in India and Burma, where the disease is very prevalent along the course of such great rivers as the Brahmaputra, the Ganges, the Indus, the Chenab, the Sutlej, the Irawadi and the Salween. Even in localities where goitre is rare, as in parts of Madras, such rivers as the Godaveri, the Kistna, and their tributaries may be associated with goitre in their upper reaches. It also occurs very commonly along the course of canals and in irrigated and marshy areas. A notable example of the importance of the marshy nature of the soil is afforded by the districts north and south of the river Ganges. In the marshy lands north of the river, goitre is excessively common; in the less extensively inundated lands south of the river, it is comparatively rare. Similar observations have been recorded in Austria and Silesia.

Association with certain Geological Formations.—While limestone and lime-bearing rocks are those most commonly associated with goitre, it can and does prevail on soils of any geological formation. The suitability of any soil for the development of this disease does not depend on its chemical composition or geological age and structure, but rather upon its organic constituents. Bircher considered that the remains of the extinct flora and fauna of limestone rocks provided these constituents, but it is not necessary that they should be derived from so remote a source. The explanation of the frequent association of goitre with limestone rocks is that they are amongst the most porous, as well as the most widely distributed, of all geological formations. They are thus amongst the most freely cultivated and inhabited, and their porosity favours the passage of the excitants of the disease to unprotected water-supplies. Waters derived from such rocks may contain an excessive quantity of lime, the ingestion of which, while it is not actually the cause of goitre, throws an additional burden on the functional resources of the thyroid gland. The presence in the soil of decaying vegetable or animal matter may convert any soil, no matter what its geological origin, into a suitable habitat for the *contagium vivum* of the disease. A manure heap or a cess-pit, for example, will be far more effective in this

direction than the remains of extinct flora or fauna. A wooden tank or a wooden cage in which fish or animals are confined, and which becomes saturated with their own alvine discharges, and with the decaying remnants of their food, a human habitation similarly soiled, all provide the conditions essential for the life of the living excitant outside the body of the goitrous subject.

Altitude.—Goitre is found at all heights above sea-level where man can live and cultivate the ground. It is to be met with in the Himalayas at all altitudes up to 10,000 ft.; indeed, of the two most goitrous villages in the Gilgit district, where there was scarcely a single goitre-free individual, one was situated at a height of over 10,000 ft. above sea-level, the other at about 8000 ft.

On the other hand, it is not absent from the sea-coast, as is often erroneously stated. It occurs in the delta of the Ganges, in the island of Cutch, on the coast near Manila Bay, in the island of Arran, in Algeria, on the shores of the Mediterranean Sea, and on the shores of the Barry estuary in Glamorganshire.

Seasonal Prevalence.—Goitre exhibits a definite seasonal prevalence, which is generally constant for any given place, but may vary in different localities. In certain parts of Himalayan India, which are not reached by the monsoon, new cases of goitre arise, and enlargements of pre-existing goitres take place during the spring and, less commonly, during the autumn months. At other seasons of the year, it is much less liable to develop.

In Himalayan localities which are reached by the monsoon, the rainy season is especially favourable to the development of the disease. The seasonal prevalence of goitre is probably related to some extent to the seasonal variation in the iodine-content of the thyroid gland; as we have seen, this is at its lowest ebb, and consequently the gland is more likely to undergo hyperplasia, during the first four months of the year. It is very probable that the seasonal variation in the gland's iodine-content may vary in different localities. In European countries, where endemic goitre is supposed to originate most commonly in the months of

March, April, May and June, the disease is sometimes called "summer goitre," or "goitre aigu." Many examples of so-called "epidemics" of goitre occurring at this season are to be met with in the literature.

Epidemic Goitre.—The most striking feature of these "epidemics" is that they arise only in endemic centres, in the neighbourhood of such centres, or in localities where the disease has previously been prevalent. They occur usually amongst susceptible new-comers to an endemic area; consequently, school children and young soldiers, especially if they are living in badly ventilated or unhygenic schools and barracks, are especially liable to be attacked. There is no essential difference between epidemic and endemic goitre. [15.]

Behaviour of the Endemic.—The endemic prevails especially in rural districts. Although it may be comparatively common in many towns, as, for example, in Innsbruck, Vienna, Berne and Bayreuth, and in Muzaffarpur in India, it is never found to prevail to such an extent as in country districts.

The endemic prevails with different degrees of intensity in different countries and in different parts of the same country. In some, the endemicity is very high; in others, "it is so widely spread over the whole country, while at the same time it is so slight, that it easily escapes notice, and cases of goitre are often considered to be sporadic, which should be more correctly classed as endemic" (Berry). Thus, while the degree of endemicity varies, it would be difficult to declare any area to be wholly goitre-free. In Delhi city, for example, which is considered to be a non-goitrous locality, I found the "endemic index" of the disease to be about 2·5 per cent. as a result of the examination of over 2,000 school-children.

Endemic Goitre is essentially a Place Disease.—In any locality in which the endemic is well marked, as in the Alps and Himalayas, it will be found that it prevails with widely different degrees of intensity in villages situated adjacent to one another.

Even in a goitrous village, occupants of certain houses, groups of houses, or institutions, may escape the disease or suffer from it in such a slight degree that it is not noticeable. This limitation of the malady to certain places is well brought out by recent experimental and epidemiological work, which has demonstrated the great importance of room, house, or place infection in the genesis of goitre. [1, 21.]

In an endemic area, the disease may fluctuate, and is subject to periods of increase and decline. It has made its appearance in many places where it was formerly unknown, and has disappeared partially or wholly from others. It seems probable that a degree of immunity to the disease may gradually develop in certain communities. Improved conditions of hygiene are usually responsible for its lessened incidence in any community.

A correct criterion of the endemicity of goitre cannot be obtained by a mere reference to the numerical ratio of thyroid enlargements, but regard must also be paid to the virulence of the disease as manifested by the presence of cretinism, deaf-mutism and its other sequelæ. A proper index, therefore, will include: (1) The number of cretinous children, deaf-mutes and idiots; (2) the number of susceptible new-comers who acquire the disease within a fixed time; (3) the proportion of men and women affected; and (4) the size and character of individual goitres. In regions where the endemicity of the disease is not high the thyroid-swelling is, as a general rule, correspondingly small, and although considerable numbers of the inhabitants may have enlarged thyroids, the large degenerated goitres are comparatively rare or wholly absent. This is very noticeably the case in certain Himalayan villages and in Switzerland and parts of Bavaria.

Cretinism, on the other hand, is usually met with in villages where the endemicity is high: in such villages the women suffer from large degenerative goitres and the hygienic conditions of life of the people are bad.

Race.—All races of mankind suffer from goitre; there appears to be no such thing as race immunity to the disease.

Among animals some species of fish appear to be very resistant to it.

Heredity.—It is doubtful to what extent heredity plays a part in the ætiology of endemic goitre. The same exciting causes which produce the disease in the parent produce it also in the fœtus and the child ; a congenital instability of the thyroid mechanism, due to the action of goitrigenous toxins on the fœtal gland, is present in a considerable percentage of all children born of goitrous mothers. Such children are, consequently, more apt to become goitrous in later life than those whose mothers are goitre-free.

Age.—In certain regions, where the endemicity of goitre is high, the disease is not uncommonly met with in breast-fed infants. In some Himalayan villages, for example, as many as 60 per cent. of infants still at the breast have been found to be goitrous. In these cases it is *congenital.*

The incidence of the disease in children varies in different endemic areas, and appears to be dependent in considerable measure on the duration of the endemic in any given locality, and upon the degree to which a natural resistance to the disease has been evolved among the indigenous inhabitants. In some regions where goitre has prevailed for centuries, visible goitres are comparatively rare in indigenous children below the age of eight years. In others, where the disease is of more recent introduction, its incidence in children of all ages is often very high, and in a locality where it is beginning to prevail cases are to be found chiefly amongst the children. [1, 15.]

When children are subjected to goitrigenous influences for the first time they are considerably more susceptible to the disease than are adults. The most susceptible age is nine years in the case of boys, ten years in the case of girls. After the age of ten, the susceptibility diminishes slightly, and again increases with the onset of puberty, a circumstance which is especially notable in the case of girls.

I have had a unique opportunity of watching the spread of

goitre in a village situated in the hill-state of Nagar in the Himalayas [15], where the disease had made its appearance for the first time, having been introduced by a goitrous family. Thirty-one cases of goitre occurred during a period of seven to eight years, amongst a population of 1,500. Of these cases twenty-nine were in young people under the age of sixteen years, the majority of whom were boys.

With increasing age, the susceptibility to goitre gradually diminishes in the case of males, but increases in the case of females during the child-bearing period of life. It rarely develops after the age of forty-five years, that is to say after the physiological atrophy of waning life has commenced. When it does so, the goitre is not, as a rule, due to hyperplasia, but to the growth in the gland of adenomata, or more rarely to malignant disease.

Sex.—Up to the age of puberty, goitre affects the two sexes almost equally; it is, if anything, more common in girls. [17.] From the age of puberty onwards, females are much more liable to suffer than are males. The sex-incidence is, however, very variable in different districts, and is dependent largely upon the severity of the endemic. Where the endemicity is slight, cases may be met with only amongst women; but in regions of high endemicity, the proportion of men to women affected may approximate as closely as one to one. [15.]

The influence of the child-bearing period of life on the development of goitre is very great. In localities where goitre is not supposed to be endemic, as, for example, in London, the thyroid gland enlarges as a consequence of pregnancy in a little less than 50 per cent. of all cases. The added strain of goitrigenous influences greatly increases this proportion, and converts these physiological swellings into pathological states.

Influence of Length of Residence in a Goitrous Locality.—Goitre may develop in as short a space of time as ten days after exposure to goitrigenous influences; this is exceptional. Amongst young susceptible new-comers to a goitrous district, a considerable proportion of cases develop within six weeks to three

months after their arrival. The liability to the development of the disease increases with length of residence in an endemic centre [17], and after a period of residence of eight years in such a centre the majority of young people under the age of eighteen become goitrous. Goitre shows a marked tendency to disappear when the sufferer leaves the goitrous district; it almost invariably reappears in such persons when they return to the infected locality.

Predisposing Factors.—Persons of a lymphatic temperament and those of a neurotic constitution, appear to be especially prone to develop goitre. New-comers to an endemic area are very susceptible to it. Other important factors, which favour its development in greater or lesser degree, fall into three main classes: (1) those which induce hyperplasia of the thyroid gland, (2) those which make undue demands upon its functional powers, and (3) those which favour the entry of the excitant or excitants of the disease into the body.

Amongst factors which may be included in the first class are attacks of certain infective diseases, notably: rheumatism, rheumatoid arthritis, malaria, measles, intestinal disorders and helminthiasis. The causal agents of these conditions or their toxic products, are all capable of inducing hyperplastic and fibrous changes in the gland, and, therefore, of impairing its normal functional resources, so that in the presence of the specific excitant of endemic goitre it may be compelled to undergo hypertrophy in order adequately to perform its functions. Amongst factors which impose an added strain upon the functional powers of the thyroid are residence at altitudes considerably above that of sea-level, defective air space, improper food or defective food-supply, puberty, sexual activity, menstruation, pregnancy and emotional states, such as fright and continued mental strain. Under all these circumstances, it is the accumulation of demand in the presence of the excitant of goitre which determines the enlargement of the thyroid gland. Amongst those factors which favour the entry of the excitant or excitants of the disease into the body are unhygienic conditions of life, residence on damp soil, and an occupation or social status which involves close and continued

contact with infected soil. It is for these reasons that goitre is much commoner amongst the labouring classes and in rural districts than amongst other classes of the community or residents in towns.

In addition to these factors, there are others which favour the action of the excitant of the disease after its entry into the body. Some of those which have already been mentioned act also in this way : intestinal disorders are of especial importance in this connection. The use, too, of waters of a high degree of bacteriological impurity, of very hard waters, or of waters holding much mineral matter in suspension, favours the onset of goitre, probably by producing abnormal states of the gastric and intestinal mucosa.

Although there is no evidence that waters holding in solution large quantities of lime are themselves capable of causing goitre, yet the ingestion of an excess of calcium throws an undue strain upon an organ whose function it is to control to some degree the calcium metabolism of the body. Such waters may therefore favour the onset of thyroid enlargement in this way.

Thus in the development of goitre a multiplicity of factors are at work, each of which adds its load to the burden which the thyroid gland is called upon to bear, and without which it may be capable of combating the specific agent which is the *causa vera* of the malady.

The Causal Agent or Agents of Goitre.—The problem of the causation of goitre is one which has exercised the minds of observers since the earliest days of medical history. There are, indeed, few diseases about which so much has been written and so many diverse views propounded. The association of goitre with mountains has led to the promulgation of many of these views. A causal influence has been attributed to configuration of the soil, to waters derived from certain soils and charged with certain chemical ingredients, to altitude, to the rarity of the atmosphere, to cold and dry air, to air holding too little oxygen and to air holding too much, to air laden with sulphurous vapours, to the action of cold air on the neck, to a want of iodine in the air, to air charged with electricity and to

some half-hundred other such-like causes. One is apt to dismiss with scant ceremony the observations of earlier observers in this field of research, but if we consider some of their views in the light of our more modern knowledge of the thyroid's function we shall realize the truth that is in many of them. The effect of altitude and of rarefied atmosphere falls into place with the gland's function of regulating the respiratory exchanges and of maintaining the red blood-corpuscles and the hæmoglobin at a level proper to the altitude. The lack of iodine in the air at altitudes above 1,000 feet will indirectly influence the thyroid towards hyperplasia by its lack in the food. The ingestion of waters charged with an excess of lime adds to the burden of the thyroid's numerous duties. Even configuration of the soil by favouring the entry of surface drainage into unprotected water-supplies is not without considerable influence in the genesis of the disease.

Within recent years the many theories as to the causation of endemic goitre have been narrowed down to those which attribute it to chemical ingredients of drinking water, to geological peculiarities of the soil imparting to the water a specific colloidal poison, to faults of nutrition, and to living micro-organisms. In a work such as the present, it is impossible to enter into a discussion of the various arguments for and against these different views. The problem was fully discussed, with respect to the evidence available up to the end of the year 1912, in the Milroy Lectures for the year 1913. [15.]

Since then I have carried out a large amount of additional experimental and epidemiological research, which has definitely demonstrated that neither chemical constituents of the water, geological peculiarities of the soil, nor factors of nutrition are primarily responsible for the genesis of this disease. It is unquestionably true that these influences may favour its development, and in this respect nutritional factors operate in marked degree, but that the true *prima causa* of endemic goitre is a living organism is now generally admitted by the majority of those who have devoted special attention to its experimental and epidemiological study.

The proof of the infectious nature of goitre may be summarized as follows :—

(1) In villages where goitre prevails, and which are situated one above the other on an unprotected water-supply, such as a mountain stream, goitre shows a steady increase in prevalence from above downwards, this increase being dependent upon the increased impurity of the water. [1.]

Experimentally-produced Goitre in the Human Subject.

Fig. 26.—Shows appearance before the controlled consumption of the residue from goitrigenous water. Circumference of neck, 33 cm.

Fig. 27.—The same subject after 30 days' controlled consumption of the residue from goitrigenous water. Circumference of neck, 35 cm.

(2) Goitre has been produced in the human subject by the experimental ingestion of the residue left on the candle of a Berkefeld filter after filtration of goitrigenous water. This residue when boiled does not cause the disease. While it cannot be said to be definitely proven that filtration through a Berkefelt filter wholly deprives the water of its goitre-producing properties, water so treated does not appear to be capable of causing goitre in man within a period of fifty-five days. The incubation period of experimentally-produced goitre in man is 13 to 15 days (figs. 26, 27). [3, 10.]

(3) The therapeutic administration of intestinal antiseptics —notably β-naphthol and thymol—is capable of causing the disappearance of recent goitres in young subjects (figs. 28, 29). This observation has been confirmed by many other workers, notably by Messerli of Lausanne. Thymol is twenty-five times as powerful a disinfectant as phenol and ten times as powerful as the cresols to *B. typhosus ;* twenty-three times as powerful as phenol in the absence of particulate matter, and seven-and-a-half times as powerful in the presence of three per cent. dried fæces (Cooper). It is thus a very powerful germicide. Now, thymol is not readily soluble in water (1 in 1,500), so that in the absence of any of its solvents—fats, oils, alcohol, and vinegar—it is sparingly absorbed into the system when administered in the form of a coarse powder. Its action in all probability is, therefore, a local one in the bowel—especially in the small bowel—and its influence in causing the disappearance of recent goitres is to be regarded as strong, though not conclusive, evidence that the habitat in man of the living excitant of goitre is the intestinal tract. [2.] Lactic acid bacillus administered daily to recent cases of goitre may cause the complete disappearance of the swelling (figs. 30, 31). [15].

(4) The restitution of the normal drainage of the bowel in persons suffering from chronic constipation and intestinal stasis associated with goitre, as by the operations of short-circuiting or colectomy, causes the disappearance or marked reduction in the size of the goitre (Lane). Intestinal toxæmia is thus shown to be the cause of the thyroid swelling.

(5) Fish confined in tanks situated one above the other on a single water-supply show an increasing proportion of thyroid hyperplasias and of visible goitres from the highest to the lowest tanks in the series (see page 41). Furthermore, the addition of pure water to the tanks, or of iodine, mercuric chloride, or of arsenic, retards or

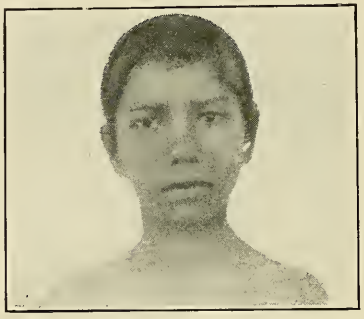
Fig. 28.—Before treatment, 42 cm.

Fig. 29.—After treatment, 36·5 cm.

Case of Endemic Goitre treated by Thymol for 3½ months.

prevents the onset of the hyperplasia, and may cause its disappearance in cases where it has arisen (Marine and Lenhart, Gaylord, 1909–12). The bacterial impurity of the water flowing from one tank to the other is, therefore, largely responsible for the onset of goitre in fish so confined. This observation confirms my findings with regard to the increase of goitre in villages situated one above the other on an open water-supply.

(6) By scraping the inner surface of the water-soaked wooden tanks in which the fish are confined, and in which the disease is endemic, an agent may be secured which



FIGS. 30 and 31.—A case of goitre before and after treatment by "Soured Milk"; duration of treatment, 30 days. Sixteen ounces were administered every morning. (Reproduced by courtesy of the Editor of the *Practitioner*).

produces thyroid hyperplasia and goitre when administered to dogs and rats, and "which from its action on the mammalian thyroid when administered through drinking water, is no doubt the cause of the disease in the fish confined in the troughs" (Gaylord, 1912). The agent is destroyed by boiling (Gaylord, 1912). The experimental production of goitre in the human subject by the method referred to above is thus confirmed.

(7) Goitre can be produced in animals—rats, goats—by feeding them on fæcal material from goitrous and even non-goitrous subjects. This observation (fig. 32) was confirmed by Sazuki in 1913, who also produced the

disease in rats by the subcutaneous injection of rats' fæces.

The results of one of my experiments are shown in fig. 32. In this case six white rats were confined in

FIG. 32.—Experimentally-produced goitre in rats. 100 per cent. of the animals consuming fæcal material developed goitre within a period of two months, the "controls" remaining normal. Figs. 11, 12, 13, 16, 22, 23 are sections of these goitres or of others experimentally-produced.

each of three equally-sized compartments of a single wooden cage. One lot received clean food and water,

and acted as controls; another received the residue left on the candle of a Berkefeld filter after filtration of an emulsion of fæces from a non-goitrous resident of a goitrous district; while the third lot received the filtrate of this emulsion. The experiment lasted two months, when, on killing the animals, it was found that 100 per cent. of those receiving fæcal material showed large-sized goitres, while the "controls" were perfectly normal. [20.]

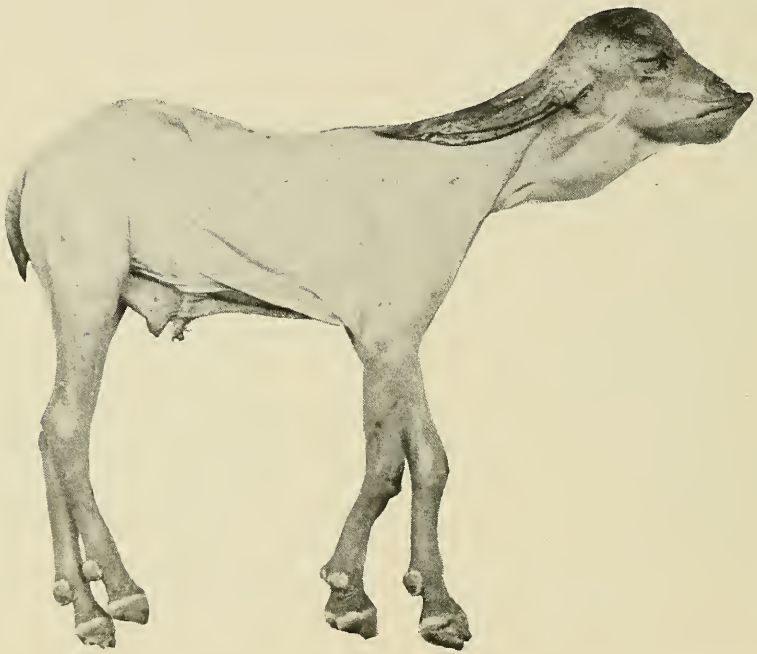


Fig. 33.—Large congenital goitre in prematurely-born goat; experimentally-produced. The animal was quite hairless.
(Reproduced by courtesy of the Editor of the *Practitioner*.)

(8) Goitre has been produced experimentally in animals—rats and goats—by feeding them on cultures, from the fæces of goitrous and non-goitrous subjects, grown under aërobic and anaërobic conditions: those grown under anaërobic conditions being the more potent in this respect. [9, 10, 20.]

(9) Congenital goitre (fig. 33), cretinism (fig. 34), and congenital

parathyroid disease (figs. 65–67), have been produced experimentally in the offspring of such animals by continuing to feed the mothers throughout pregnancy with these cultures. [16, 24, 25.]

(10) Finally, vaccines prepared from intestinal organisms are capable of causing the disappearance of recent cases of

EXPERIMENTALLY-PRODUCED CRETINISM.

FIG. 34.—Litter of three young rats, aged 20 days ; the offspring of a mother which consumed goitrous fæcal filtrate prior to, and during, pregnancy. The animal in the centre is a cretin. Note stunted growth and curvature of spine.

goitre when injected in appropriate doses at weekly intervals (figs. 37, 48). [14.]

This accumulation of facts demonstrates, I believe, that the causal agents of goitre, as well as of its congenital manifestations, are micro-organisms inhabiting the alimentary tract

of sufferers from this disease, and often of other persons whose thyroids show no actual enlargement, but which nevertheless may be in a hyperplastic state. Except in so far that all the epidemiological and experimental facts point to anaërobic organisms as the causal agents of this disease, they do not permit of a more definite conclusion as to the identity of these organisms.

It is amply proven also that the changes characteristic of parenchymatous goitre are due to toxic action and not to the presence in the gland of living micro-organisms. The goitrous thyroid of endemic localities is invariably sterile.

It has been shown that goitre is essentially a place disease, and that it is intimately associated in its origin with dirt. The organisms, which are capable of causing it, live in the soil of infected localities, and particularly in soil which contains a high proportion of organic matter of human or animal origin. They are present especially in and around unclean human and animal habitations; they cling to certain houses, rooms, stables, byres, animal-cages or fish-tanks in which the excrement of the inhabitants is allowed to accumulate. They are capable of life in waters which are grossly polluted and show a high bacterial content, but in pure water, or water exposed to the purifying influences of sedimentation, oxygenation, and sunlight, their life is comparatively short, and their powers of multiplication very limited.

These organisms reach the alimentary tract of man and animals by means of infected soil, food, or water, and there they flourish and produce toxins which, on absorption into the blood-stream, initiate the goitrous changes in the thyroid gland. Soil, water, and food are, therefore, vehicles only whereby the infecting agent or agents reach the body of men and animals. It seems almost certain that the great source of the disease is the infected individual, and that he is the producer, the reservoir, and the distributor or "carrier" of the infecting agents. These agents are discharged from the body in the fæces, and, it may be, in other ways not known to us, as, for example, in the urine[1] and saliva. If they reach

[1] Experiments directed towards producing goitre in rats by means of the urine of goitrous persons have, in my hands, yielded negative results.—R. McC.

a damp soil containing a high proportion of organic matter, they live and, it may be, multiply; while if they reach an organically impure and stagnant water which is protected from the purifying effects of light and air, as in the case of many wells ("goitre wells"), they may survive for a considerable time.

All the evidence at present available points to these as the common modes of infection; but there may be other means whereby the living excitants of the disease are conveyed from the sick to the healthy. It is possible, for example, that flies may act as the conveyors of the infection to man. There is no evidence at present available to suggest that any ecto-parasite, biting insect, or worm acts as a host for the further development of the living excitant of endemic goitre outside the body of man and animals. [20.] The very wide distribution of the disease in the animal kingdom renders such a mode of spread improbable. In their manner of origin and spread, endemic goitre and typhoid fever closely resemble one another. The conditions which are favourable to the development and spread of the one are equally favourable to the other.

SYMPTOMS AND COURSE OF THE DISEASE

The histo-pathology of endemic goitre having been sufficiently dealt with in the foregoing section, we may now proceed to a consideration of the symptoms and course of the disease.

The goitre, which is soft in consistency, is, as a rule, a uniform enlargement, though occasionally one or other lobe may be the more prominent. In the latter case the more prominent lobe is usually the right. There is not infrequently considerable pulsation in the vessels of the neck. The swelling does not, as a rule, progress in size in a uniform manner, but varies considerably from time to time. It may even disappear for a time, only to reappear again at a later date. Goitres at this stage are rarely large. The swelling is unattended by symptoms other than the subjective sensation of fulness in the throat. The enlargement, after attaining a certain point, usually subsides to a size at which it remains stationary.

Spontaneous recovery in young subjects while the patient continues to live in the endemic area, is not uncommon. It has been found to occur in 11 per cent. of cases in boys and 7 per cent. of cases in girls of the Lawrence Military Asylum at Sanawar, in all of whom the swelling was of small size and probably very largely due to physiological causes. Such spontaneous recovery appears, in some cases, to confer a degree of immunity against recurrence. [17.] Incipient goitres very commonly disappear spontaneously when the patient leaves the goitrous locality.

Such a train of events is what may be called a " first attack " of goitre. The tendency is for the gland to revert to a condition approaching as nearly to normal as is possible. In some few cases the reversion may be complete, but in the great majority the " attack " leaves the thyroid larger than it found it.

The immunity which is probably conferred by such an attack of goitre is of a very transitory character. With succeeding springs and autumns, in parts of Himalayan India, recurring attacks of thyroid hyperplasia occur, and the gland increases in size by a step-like process, which was also described by Lawson Tait in the case of goitre associated with pregnancy. The process is comparable to that which takes place in the spleen as a result of successive attacks of malaria. If the patient is subjected to goitrigenous influences for any length of time, degenerative processes soon make their appearance, and the large cystic and adenomatous goitres which are so common in goitrous localities are the result. Should the subjection to goitrigenous influences be intermittent, the onset of degenerative processes is much longer delayed, and these changes are much less evident than in the case of persons who reside constantly in a goitrous locality.

Symptoms referable to marked disturbances of the function of the thyroid are almost completely wanting in endemic goitre, but in many cases slight evidences of its sluggish action can be detected. Compare, for example, the appearance of the face in cases before and after cure (figs. 30, 31, 37–47).

In long-standing cases in which degenerative change has occurred, more obvious symptoms of hypothyroidism may

occasionally be observed. Tetany is not uncommon in certain parts of the Himalayas among women suffering from degenerated goitres. Such symptoms as occur are mainly referable to the effects of pressure on the important structures in the vicinity of the gland. Respiratory disturbances may be present, and are due to mechanical constriction of the trachea, more rarely to mechanical injury to the nerves of the larynx.

Functional disturbances of the heart, resulting in dilatation and hypertrophy of the right heart, may be due partly to mechanical impairment to the venous circulation (Rose's goitre-heart), partly to hindrance of respiration (Kocher's goitre-heart with dyspnœa), and perhaps also to compression of the cardiac nerves. Bircher has attributed to the toxic agents of endemic goitre a definite action on the heart, which results in its enlargement and in an increase in the thickness of the walls. I have found the widest variations in the size of the heart and in the thickness of its walls in rats, and have not observed that this variation has borne any definite relationship to the presence or absence of a goitre. A considerable experience of endemic goitre, in India and Europe, leads me to believe that the heart is not affected in simple goitre, except as a result of the mechanical effects of the enlarged thyroid. When an apparently simple goitre is associated with cardio-vascular symptoms, which are not due to the effect of pressure, the condition is probably one of incipient Graves' disease, and search should be made for other evidences of this malady.

THE BLOOD IN GOITRE

Blood-changes of a fairly definite character occur in endemic goitre. The number of erythrocytes is diminished, as well as the hæmoglobin-index. The coagulability of the blood is increased. The total number of leucocytes is reduced. The polymorphonuclear leucocytes are constantly below normal limits; the absolute reduction in their numbers may be 50 per cent. of the normal. They may form as little as 30 per cent. of the leucocytes in peripheral blood; the average differential

count in 73 cases was 46·5 per cent. The small mononuclear cells are usually above normal limits; the absolute increase in their numbers may be twice that of the normal. In differential leucocyte counts they may form as many as 45 per cent. of the total leucocytes in peripheral blood; the average count for 73 cases was 32·2 per cent. The eosinophile cells are usually increased in numbers and may form as high a proportion of the total leucocytes in peripheral blood as 20 per cent.; the average count for 73 cases was 10 per cent. The large mononuclear cells are usually within normal limits. [2.]

The blood-changes of exophthalmic goitre resemble those of endemic goitre, in that the polymorphonuclear cells are diminished, and the mononuclear cells are increased in numbers. There is, however, no blood-picture which can be said to be characteristic of either Graves' disease or of simple goitre, so that the employment of the so-called "blood-picture test," in the differentiation of cases of simple goitre from atypical cases of Graves' disease, is valueless, and calculated to lead both to errors of diagnosis and to the adoption of surgical methods of treatment which are not justified by the gravity of the patient's condition. [15.]

No organisms of a bacterial or protozoal nature, which can be considered as causal agents of the disease, have been found in the blood or thyroid glands of cases of endemic goitre. [15.]

Prophylaxis.—Goitre is mediately infectious, but non-contagious. Man and his domestic animals are the great source of the disease, their habitations are centres of infection, and all food-materials which, directly or indirectly, have been soiled by their excreta may be vehicles for its spread. Contact with the infected individual is of importance, in so far as it affords opportunities for the transference of the infecting agents from the sick to the healthy. Soil and water are the main vehicles whereby this transference is effected, and their influence in this connection has been abundantly shown by experiment. Infected soil is the more important of the two, since the life of the infecting agent is probably much longer in damp and organically polluted soil

than in water; it is from the soil also that a water derives the noxious agents.

It is very necessary, therefore, to avoid contamination of the hands and of the food by the soil of infected localities. Food should be protected from flies, and should be prepared by non-goitrous persons of cleanly habits, who presumably are not "carriers" of the infection. Drinking-water should be sterilized by boiling or by such chemical agents as chlorine or iodine. [17.] That the importance of this measure is great is shown by the fact that the addition of perchloride of mercury (1–4,000,000) to the water in which trout are artificially-reared effectually prevents and cures the goitre from which these fish are so liable to suffer. In some localities the consumption of certain waters appears to prevent the development of the disease; these waters usually contain small amounts of iodine, and are of a high degree of bacteriological purity. [22.] (See also Appendix.)

The improvement of personal hygiene, the provision and maintenance of sanitary dwellings and of pure and well-protected water-supplies, the institution of hygienic systems of conservancy, the proper disposal of sewage, the removal of stables and byres from the neighbourhood of human habitations, the abolition of cess-pits and of manure-heaps in the immediate vicinity of dwellings, are measures which will result in the diminution or disappearance of the disease in all goitrous localities.

Treatment.—The treatment of goitre depends upon the stage to which the disease has progressed. Medicinal measures are applicable only to cases of comparatively recent origin; when secondary degenerative changes—cysts, adenomata, fibrosis, and calcification—have become ingrafted upon the initial process of thyroid hyperplasia, medicinal treatment is of little or no avail, and the case must be dealt with by surgical means. It is with the non-operative treatment of goitre that I propose to deal.

When goitre has developed in a locality where the disease abounds, cases of recent origin and of small size, especially in young people, often disappear spontaneously when the patients

are removed to a non-goitrous locality. Residence at the sea-coast is often of considerable curative value in such cases. It is to be remembered that persons who have once suffered from goitre are prone to a recurrence of the swelling, should they again reside in a goitrous district. Change of residence is, how-

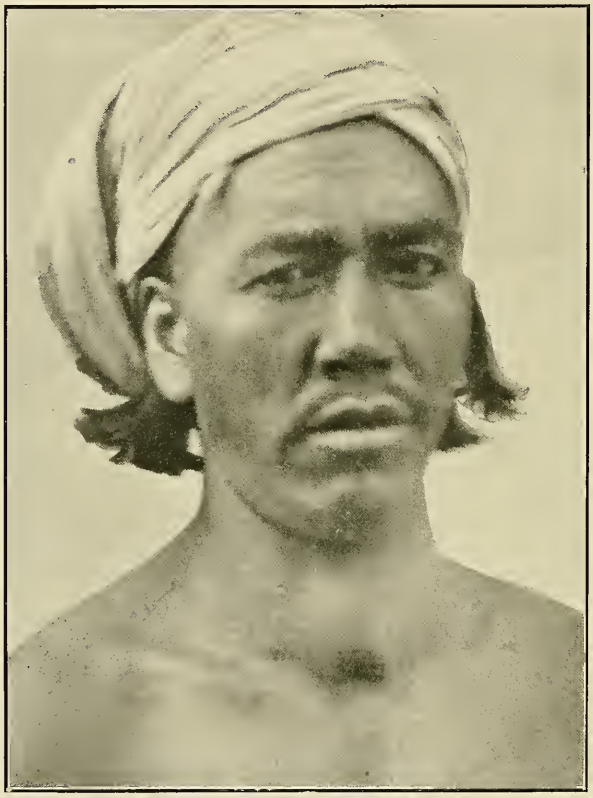


Fig. 35.—Case of endemic goitre, containing small nodule in isthmus, before treatment by thymol. Circumference of neck, 40½ cm.

ever, a measure which is not practicable in the majority of cases. Under such circumstances, treatment should be directed to the removal of the exciting cause of the disease, and of the factors which favour its action.

In dealing with the exciting agent or agents of goitre it is necessary (1) to prevent their entry into the body, and (2) to

destroy or diminish the number of those which already exist therein. We must, therefore, correct all unhygienic conditions of life, advise the use of boiled water or of water which has been sterilized, and instruct the patient to avoid the contamination of the food by soil-infected hands. Of remedies which may be

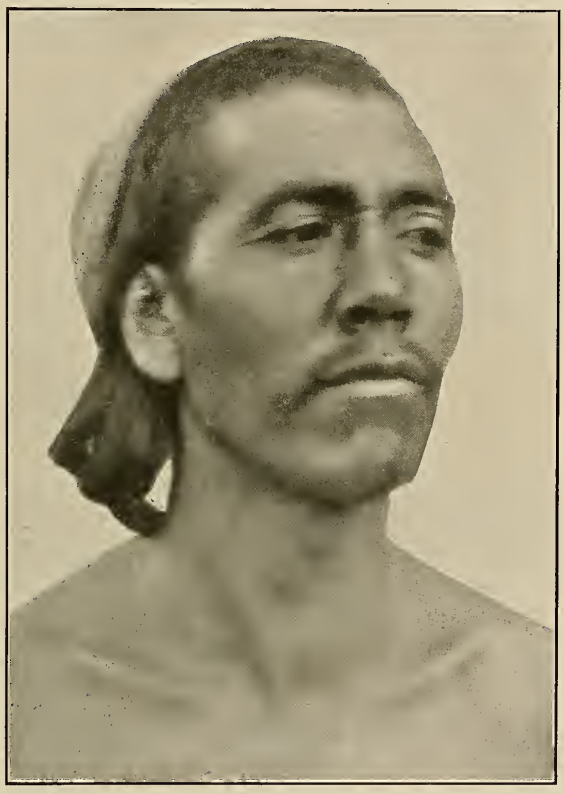


Fig. 36.—The same case after treatment by thymol. Circumference of neck, 37 cm. The swelling has completely disappeared, except for the nodule in the isthmus.

employed to destroy or to reduce the numbers of goitrigenous organisms or their toxins in the alimentary tract, the most important are the antiseptics—iodine, thymol, salol, β-naphthol, benzo-naphthol, quinine, hydrofluoric acid, the bacillus bulgaricus —and vaccines.

Iodine is the most potent of all known remedies in the

treatment of parenchymatous goitre. It possesses the specific property of causing the thyroid to revert to the colloid state ; its action is also anti-toxic and anti-septic. It is best given in the form of the tincture, either alone or combined with iodide of potassium, or as Syrup ferri iodidi. The drug must be administered in sufficiently large doses to be efficacious, but the smallest dose which produces the desired effect is the dose to employ. Five minims of the tincture, combined with five grains of the potassium salt, is a suitable initial dose. This may, if necessary, be gradually increased till the patient is taking three or four times as much. Care must be taken to stop the administration of iodine, if symptoms of iodism are produced or if the digestion is upset. It is to be remembered that the indiscriminate use of iodine may precipitate the onset of symptoms resembling Graves' disease (" Iodine-Basedow " of German authors). When prescribed in suitable doses, its effect on parenchymatous goitre is obvious within a month. If it produces no good effect in this time, its continued use is not likely to be beneficial.

Iodine may be applied externally over the enlarged thyroid, either in the form of the biniodide of mercury ointment, diluted if necessary, or of the tincture. The ointment is much used in India, where the patient is instructed to rub it well into the neck, and to sit exposed to the sun for one or two hours. A few such applications often result in marked reduction in the size of the swelling. The external application of iodine is a useful adjunct to other forms of medication. The application of liq. epispasticus so as to cause blistering of the skin over the gland is also often useful.

Intestinal Antiseptics.—Of these the most potent is *thymol.* It is given in doses of 10 grains or more night and morning, and is best administered in the form of a coarse powder, washed down by a draught of water. The bowels should be kept active by the occasional use of salines, and all solvents of the drug must be excluded from the dietary. In recent cases of the disease, the beneficial effects of this drug are often very striking (figs. 28, 29, 35, 36). The dietetic restrictions attending its use make it more

suitable for cases of the disease amongst Indians than amongst Europeans. In the latter, *salol*, *β-naphthol* or *benzo-naphthol* are more convenient, but less efficient remedies. They may be administered in full doses twice or thrice daily. Large doses of quinine are often useful in early cases of goitre, and dilute hydrofluoric acid (1 in 500), in doses of 20 to 60 minims, has been employed with success in its treatment. "*Soured milk*," prepared from a good strain of the Bulgarian bacillus, is a useful remedy, either alone or as an adjunct to other forms of medicinal treatment (figs. 30, 31).

Autogenous *vaccines*, [14] prepared from intestinal organisms belonging to the colon group, have been employed successfully in the treatment of recent cases of goitre (figs. 37–42). These vaccines should be administered in increasing doses, varying from 150,000,000 to 1,000,000,000 of the organism, at intervals of one week.

Staphylococcus vaccines have also proved efficacious in causing the disappearance of goitre, when administered in doses of from 250 to 500 millions once a week (figs. 43–45). It is advisable to administer these vaccines in doses sufficiently smart as to produce a slight rise of temperature.

Figs. 46–48 illustrate the result of treatment by a vaccine prepared from the spore-bearing organism to which reference has previously been made (page 54). This result is of peculiar interest, inasmuch as the toxins of this organism were shown by experiment to be capable of producing tetanic spasms in dogs, and of causing the most marked destructive changes in the thyroid gland (fig. 9). [8, 9, 10, 11.]

While there is at present no conclusive evidence that any one of the organisms whose vaccines have been employed in the treatment of goitre has a specific influence in the production of the endemic form of this disease, it is well proven that they all possess in greater or lesser degree the power to induce hyperplastic and, in the case of the spore-bearing organism, fibrotic changes in the thyroid gland. It is quite possible, therefore, that in certain cases any one of these organisms may be the actual excitant of thyroid enlargement. Such cases are those associated

with definite symptoms of intestinal toxæmia and stasis, to which I shall refer at greater length under the term "Toxæmic Goitres." There must exist, however, a specific organism of endemic goitre,

Fig. 37.—Before treatment, 38·5 cm.

Fig. 38.—After treatment, 36 cm.

Case of endemic goitre treated with autogenous "mixed" vaccine containing coliform organisms from the intestine.

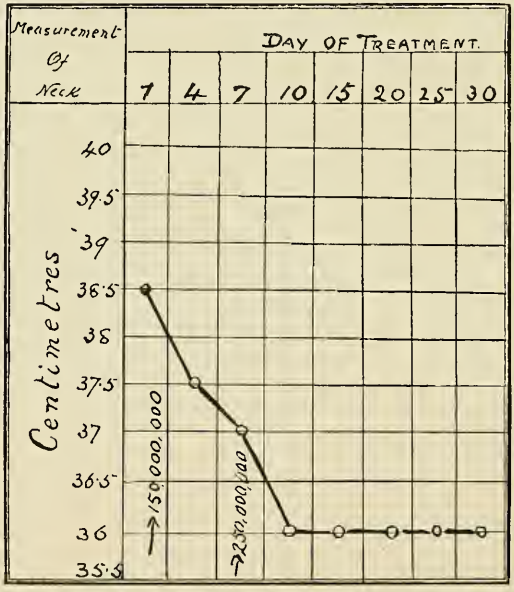


Fig. 39.—Chart showing measurements of neck at various stages of treatment, with doses and times of administration of the vaccine.

and on the assumption that no one of the vaccines which I have employed contains this organism, my explanation of their action

would be that, by aiding the disappearance of secondary infections, they relieve the thyroid of part of its abnormal burden and enable it, without continuing in a state of hypertrophy,

Fig. 40.—Before treatment, 42 cm.

Fig. 41.—After treatment, 37·5 cm.

Case of endemic goitre treated with autogenous *B. Coli* vaccine.

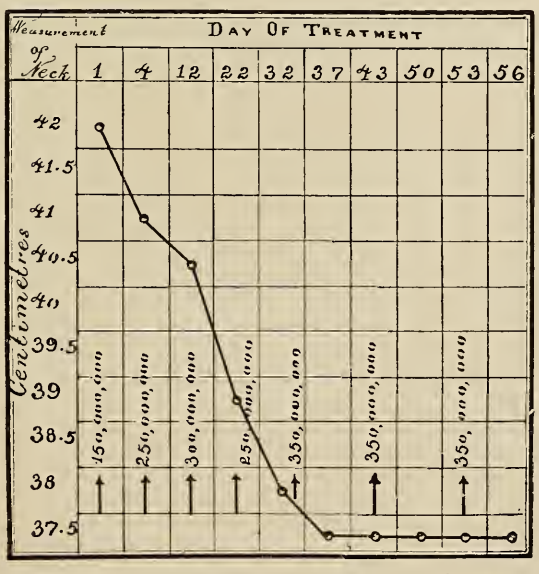


Fig. 42.—Chart showing measurements of neck at various stages of treatment, with doses and times of administration of vaccine.

successfully to combat the specific toxin of goitre. Such an explanation may prove to be wholly unnecessary when we are in possession of some more definite knowledge as to the mode of

action of vaccines in general—a subject concerning which we are still profoundly ignorant.

An effective measure in the treatment of goitre consists in excluding the operation, or counteracting the effect, of those

FIG. 43.—Before treatment, 39 cm.

FIG. 44.—After treatment, 36 cm.

Case of endemic goitre treated with *Staphylococcus aureus* vaccine.

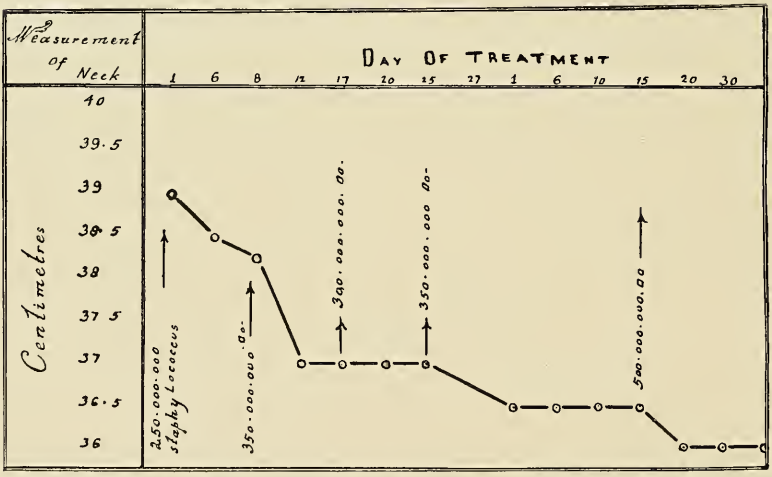


FIG. 45.—Chart showing measurements of neck at various stages of treatment, also doses and times of administration of the vaccine.

factors which favour the action of the excitants of the disease by making undue demands upon the functional powers of the thyroid gland. The patient should, therefore, live under the best possible hygienic conditions of life in large well-ventilated

rooms or in the open air, and at an altitude as near sea-level as possible. The dietary should be largely vegetarian, meat being restricted to once in the day. Constipation and intestinal disorders

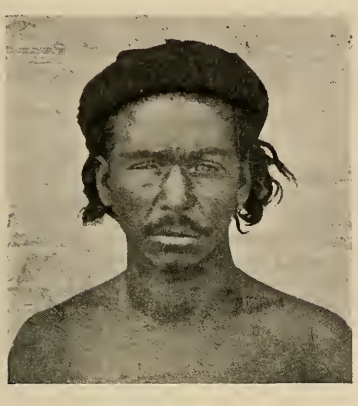


FIG. 46.—Before treatment, 41 cm.

FIG. 47.—After treatment, 37·5 cm.

Case of endemic goitre treated with vaccine made from spore-bearing organism isolated from fæces of goitrous horse.

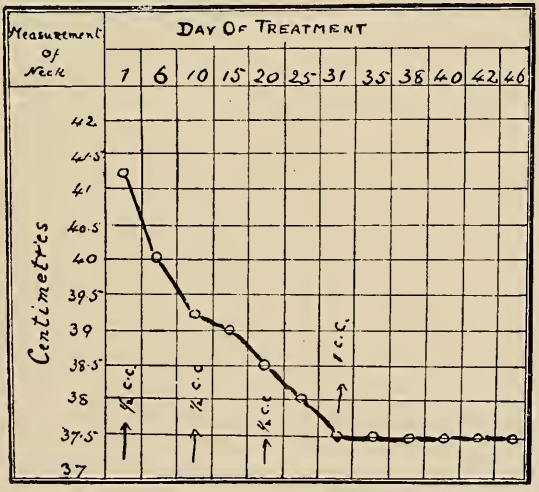


FIG. 48.—Chart showing measurements of neck at various stages of treatment, with doses and times of administration of vaccine.

must be corrected, and the bowel freed of parasitic worms if these should be present.

The patient must lead a life which does not excite the emotions, and, finally, in cases associated with the onset of puberty or of

menstruation, and in those which persist after pregnancy, some preparation of thyroid extract should be administered. The liquor thyroidei (B.P.) is the most efficient of the preparations of the gland, but when this is not available, the fresh tabloids are very convenient and effective. They may be administered in doses of 2–5 grains combined with 10 grains of bicarbonate of soda at bed-time. Many cases of the disease, especially in young girls, respond readily to this treatment, combined with attention to the bowels; this is often all that is required to cause the disappearance of the swelling. Thyroid preparations act mainly by providing the gland with iodine in a readily assimilable form, and thus easing the strain on its activity; they also possess a specific influence in regulating the gland's functional capacity. They are often ineffective where there is much intestinal fermentation, so that it is well, when employing them, to put the intestinal tract into as healthy a state as possible by the use of appropriate remedies. Indeed, if this is not done, the most efficient of thyroid preparations may be rendered void of beneficial action.

Thyroid extract is sometimes effective in cases which are not influenced by iodine. Its potency is increased by its combination with potassium iodide, grey powder, bicarbonate of soda, or with arsenious acid in small doses; these adjuncts to thyroid medication (mercury and arsenic) should not, however, be administered for periods of over a fortnight at a time. The initial dose of thyroid gland preparations should in all cases be small, and should be increased with caution. The smallest dose which produces the desired effect is the dose to employ. When tabloid or other preparations are prescribed, care should be taken to ascertain their precise strength in terms of iodine-content. Cardiac weakness is a contra-indication to their use, unless when due to hypothyroidism (see page 185).

One or other, or a combination of these measures, will effect a cure in the majority of recent cases of simple goitre. Cases are occasionally met with, however, which, though apparently suitable for medicinal treatment, resist all measures which are employed; they are probably those in which a considerable degree of fibrotic change has occurred.

SECTION 2

EXPERIMENTAL CONSIDERATIONS DEALING WITH THE CONGENITAL MANIFESTATIONS OF GOITRE

To obtain a clear conception of the genesis of the congenital manifestations of endemic goitre, it is necessary to refer to the results of certain experiments carried out on rats, dogs, and later on goats, during the years 1911–1914. [16, 25.] We have seen that goitre can be produced experimentally in these animals by feeding them on cultures of fæcal organisms from goitrous and even from non-goitrous persons living in endemic districts, and by the filtrate and residue of fæcal emulsions from these persons. When such cultures or fæcal material were administered to rats throughout the course of pregnancy, and the thyroid glands of their offspring were subsequently examined, the following results were observed :—

(1) A small proportion, 4 to 5 per cent., were born cretins, that is to say, they were born with complete fibrosis of the thyroid and parathyroid glands ; but this result was only observed to occur among the offspring of goitrous rats fed on fæcal material from *goitrous* persons, pointing to the specific nature of the toxic excitant (figs. 25, 34).

(2) Approximately 63 per cent. were born with congenital goitre. This result was observed amongst the offspring of goitrous rats receiving aërobic or anaërobic cultures from the fæces of goitrous persons : the latter being the more potent to cause the condition.

(3) Approximately 32 per cent. were born with congenital disease of the parathyroid glands. This result was observed only amongst the offspring of goitrous rats fed during pregnancy on *anaërobic* cultures from the fæces of goitrous persons, or on the

fæcal filtrate from such persons, a finding which points to the specific action of the products of these micro-organisms.

(4) Approximately 33 per cent. were born with normal, or relatively normal, thyroid and parathyroid glands.

(5) Where there was congenital disease of the parathyroid glands there was also congenital disease of the thyroid gland.

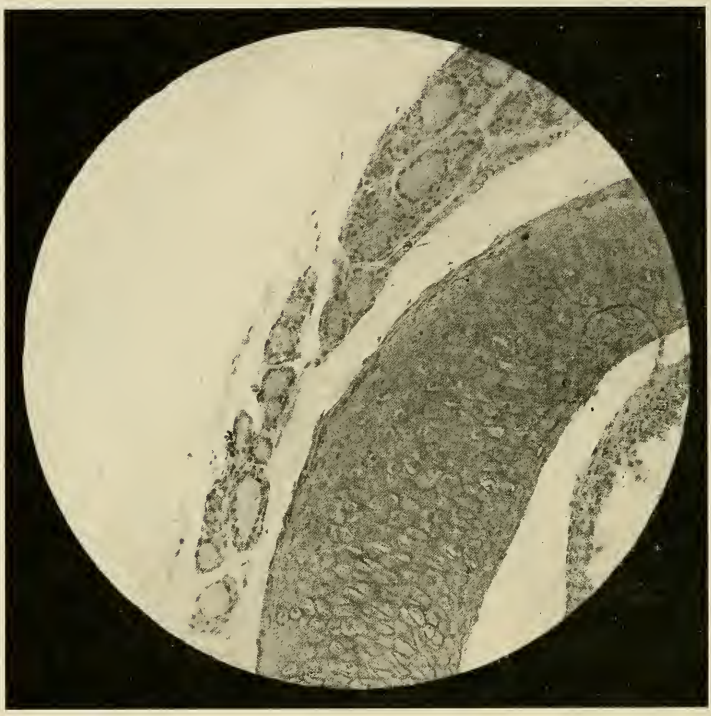


Fig. 49.—Section of normal thyroid's isthmus from a 4-day-old rat. × 180. Same case as Fig. 66.

In rare cases, however, the thyroid was less severely affected than the parathyroid.

In no case did any of the numerous offspring of the control animals exhibit thyroid fibrosis or parathyroid lesions.

These findings admit of the following conclusions :—

(*a*) As congenital parathyroid disease is comparatively common amongst the offspring of goitrous rats, it is presumable that it is also comparatively common amongst the offspring of goitrous human beings.

(*b*) Congenital parathyroid disease is due to the action on the fœtal parathyroid glands of the toxic products of *anaërobic* organisms absorbed from the maternal intestine.

(*c*) Congenital goitre is due to a like cause, but the thyroid swelling may be induced by organisms capable of growth under aërobic or anaërobic conditions—the latter being the more potent.

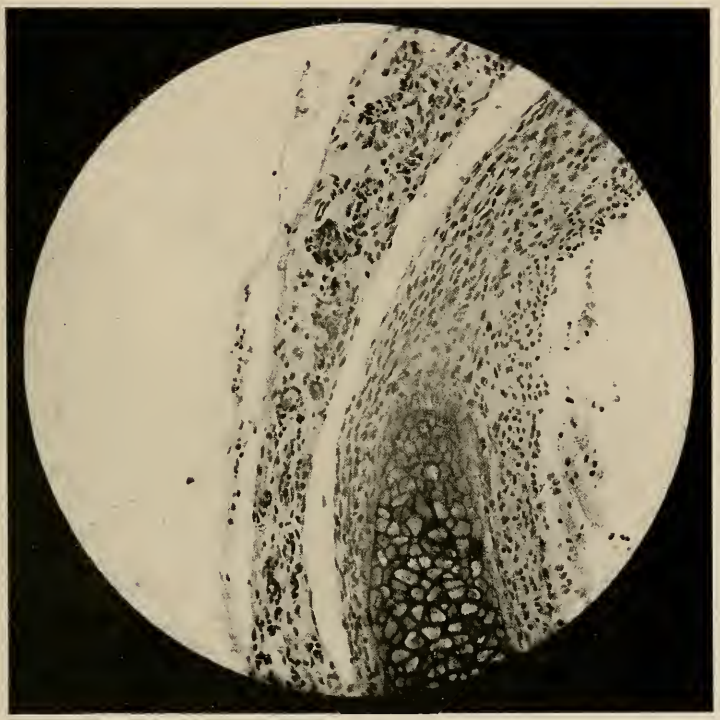


Fig. 50.—Marked hyperplasia and fibrosis of thyroid's isthmus. From a 4-day-old rat. Mother fed on fæcal filtrate before and during pregnancy. Same case as Fig. 67. × 180.

(*d*) Cretinism is due to the action on the fœtal thyroid apparatus of specific poisons produced in the maternal intestine.

These poisons are capable of causing complete destruction of the fœtal gland in only a small proportion of cases. In the case of cretin rats (fig. 34), the parenchyma cells of the thyroid and the parathyroid glands are completely replaced by fibroblasts (fig. 25). As a rule, however, less extreme degrees of thyroid defect are produced, and it is interesting to note that the isthmus of the gland

is very liable to be first affected by the process. It is early converted into a band of fibrous tissue (figs. 49, 50), while the lobes may be involved to a lesser degree. The failure to feel the isthmus of the gland in the human subject, which is so commonly regarded as a test of the thyroid's atrophy, may thus be an early sign of its fibrosis, but it is to be remembered that the lobes may not be affected to the same degree as the isthmus, and that clinically it is impossible to feel the thyroid in a large number of healthy people.

The lesser degrees of thyroid impairment, which resulted from these experiments, afford an explanation for the many varying degrees of cretinism and cretinoid states met with in goitrous districts, while the parathyroid lesions, as we shall see, are largely responsible for the nervous symptoms from which many cretins suffer.

Similar experiments in goats [24, 25] have resulted in the formation of enormous congenital goitres in the offspring (figs. 33, 53), and have abundantly confirmed the findings in rats with regard to this peculiar manifestation of the goitre noxa. Unfortunately, the outbreak of war prevented the complete study of the thyroids and parathyroids in these animals, but sufficient work was done to demonstrate that the toxic products of certain fæcal organisms possess the property, not only of inducing the development of large goitres in the fœtus, but also of retarding fœtal development and bringing about its premature cessation and the discharge of the fœtus from the uterus.[1] This finding is of the utmost importance, not only in regard to its bearing on the genesis of congenital goitre, but also as indicating what must be in modern woman a frequent source of intra-uterine death of the child. The frequency with which such an unfortunate event occurs in women who are sufferers from grave toxæmias is well known, but it is not so generally recognized that bacteria inhabiting the intestinal tract may be a source of such toxæmias.

[1] In these experiments, twelve goats fed on fæcal cultures throughout pregnancy, gave birth to eleven kids with congenital goitres. They were born prematurely and all were hairless and ill-developed. The horny part of the hoof was quite undeveloped. [25.] See Appendix.—R. McC.

As illustrating the effect of the toxic products of intestinal bacteria in producing tetanoid symptoms, an experiment which I carried out on dogs, in 1911, may be of interest.

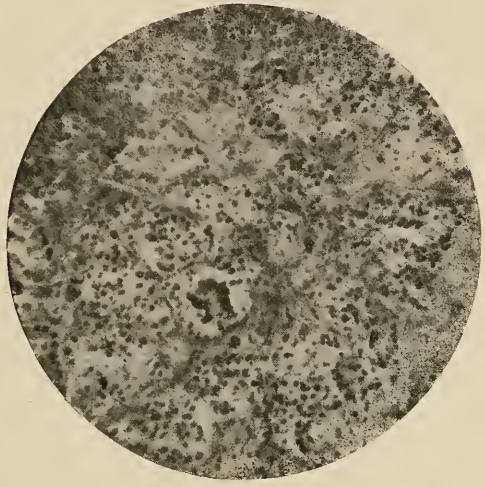


FIG. 51.—Experimentally-produced atrophy in thyroid of dog; note complete absence of colloid except for one inspissated mass, disappearance of alveolar structure, destruction and desquamation of cells, invasion by fibroblasts and commencing formation of young fibrous tissue. × 500.

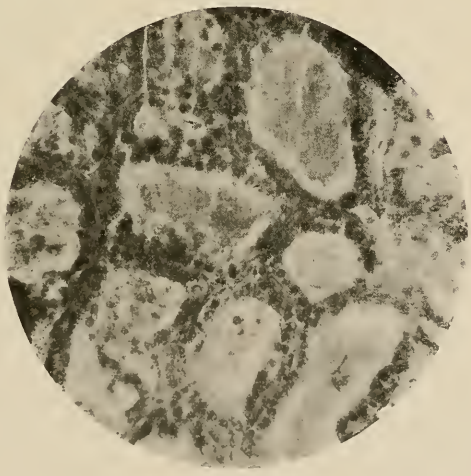


FIG. 52.—Normal thyroid gland of dog. Note vesicles lined by single layer of epithelium, abundance of colloid. × 500.

These dogs were each given nine 48-hour agar culture tubes from which the growths of the intestinal spore-bearing organism,

which had been obtained from the fæces of a goitrous horse (see p. 54), were washed. One of these animals developed spasms of the limbs, which lasted for six hours and did not recur; a second was unaffected; in a third the animal became stiff and unsteady in his limbs about six hours after he had eaten the culture-material. On the following day he developed pronounced spasms of the muscles of the limbs and tail. He was unable to stand, and when propped up his legs gave way under him. These symptoms persisted, the animal lost consciousness, a blood-stained discharge from the mouth, nose, and anus appeared on the fourth day, and he died on the ninth day of the experiment. The thyroid lobes were removed with two enlarged lymph glands in the vicinity. From the latter the original spore-bearing organism was recovered. The thyroid showed on macrosopical and microscopical examination the following pronounced changes : it was greatly reduced in size, being only about one-third of the size and weight of the thyroid of a control, but slightly heavier, dog. The organ was almost wholly cellular with occasional vesicles scattered here and there throughout the section. Newly-formed fibrous stroma was abundant, and was represented by a well-marked network of fibroblasts, the meshes of which were filled with degenerating parenchyma cells. Colloid was wholly absent except in a few scattered vesicles. These appearances are seen in fig. 51, and are well brought out by comparison with the control animal's gland (fig. 52). I did not at the time realize the importance of the observation, and failed to examine the parathyroids. [10.]

With this preliminary consideration of the results of experiments in animals, we may now proceed to inquire how far they account for the occurrence and course of the congenital manifestations of the goitre noxa in the human subject. These manifestations are : congenital goitre, cretinism, congenital hypothyroidism, and parathyroid disease.

SECTION 3

CONGENITAL GOITRE

Congenital goitre is extremely common in villages where the endemicity of goitre is high. Thus, in certain Himalayan villages, where every woman and almost every man is goitrous, as high a percentage as 60 per cent. of cases of congenital goitre in breast-

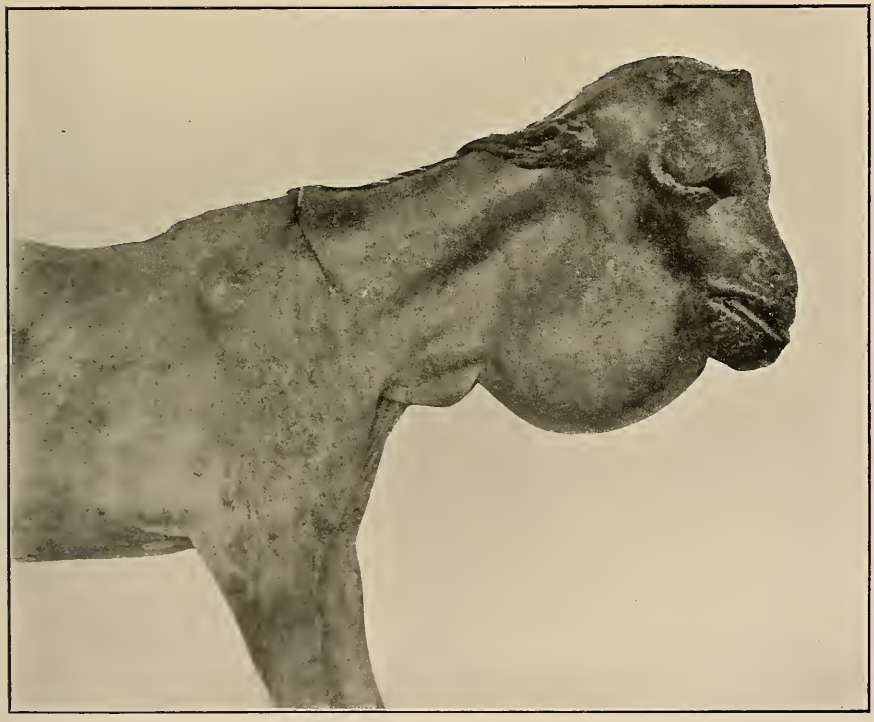


Fig. 53.—Large congenital goitre in prematurely-born kid; experimentally-produced. Mother fed on cultures of fæcal bacteria before and during pregnancy.

fed infants has been found. [1.] It is interesting to note that this figure corresponds very closely to that found in experimentally-produced cases in rats (63 per cent.).

In such villages the percentage of abortion among women, and the infant mortality, are very high, so that the actual percentage of cases born with goitre is probably considerably higher than 60 per cent.

In villages, on the other hand, where the endemicity of the disease is lower, congenital goitre is not so common.

The mothers of children born with congenital goitre are often myxœdematous to some extent. They commonly suffer from tetany.

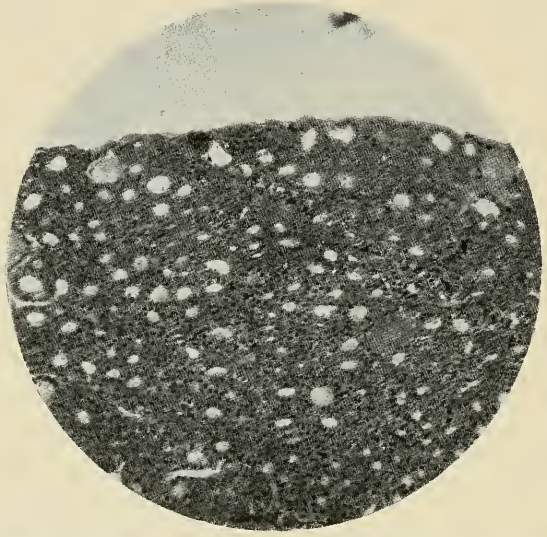


Fig. 54.—Section of thyroid from a case of congenital goitre in 30-day-old rat. Parents fed on fæcal filtrate before and during pregnancy. Note great proliferation of parenchyma. Very small vesicles; little colloid in vesicles. Invasion of gland by fibroblasts. ×90.

Congenital goitres are usually uniform enlargements of small size, which tend to disappear spontaneously a few months after birth. In animals in endemic areas, in which congenital goitre is also found, the disappearance of the swelling after birth is commonly very rapid. Occasionally, however, the goitre may be very large (fig. 53), or so large as to impede delivery.

Congenital goitre is much more commonly found in the poor and ill-nourished classes.

It is rare in cretins. Indeed, in my series of 203 cretins only two cases of goitre were found before the age of three years.

The histological features of congenital goitre resemble those of other hyperplasias of the thyroid. There is an enormous over-production of parenchyma tissue, the organ is very cellular and cuts like liver, the vesicles are small, and an abundance of colloid lies between the parenchyma cells and in the lymph spaces (fig. 54).

The condition is one which rarely calls for treatment; sufferers either die shortly after birth, or at birth, or they recover spontaneously; in rare instances they may become myxœdematous under continued toxic provocation.

Where treatment is called for, thyroid extract may be administered to the mother if the child is being breast-fed, so that she may benefit by it as well as the child, or small doses, ♏ 1–2 of the B.P. Liquor at night, may be given to the child. If the goitre is large and impeding breathing, it may be dealt with surgically; there are records in the literature of a few such cases.

SECTION 4

ENDEMIC CRETINISM [1]

Illustrations of the high percentage of cretinism in certain goitrous districts have already been given. It is most common and of a more severe type in villages where the endemicity of goitre is high, that is to say, where the adult sex-ratio of goitre distribution approaches one to one. Its incidence is determined by the age of the endemic of goitre and by the incidence of goitre in the adult population.

It does not make its appearance in a goitrous family until the second or even the third generation. It shows a marked tendency to occur in certain families. Thus, it is common to find several, and sometimes every child in the family, cretinous. Consanguinity plays a most important part in determining the family character of the disease.

Males are more commonly cretinous than females. The proportion is as five of the former to two of the latter. The preponderance of males over females is still maintained among cretins who are also goitrous, but it is much less marked, the proportion then being 5 to 4.

Just as endemic goitre *per se* is rarely found to produce grave myxœdema in the adult, so this condition, when it develops in the child, does not cause it to become cretinous. The unaided action of the goitre noxa in the individual rarely does more than to produce slight signs of thyroid defect; but in the presence of other nutritional, psychic or infectious factors, juvenile myxœdema may arise in a small proportion of cases. It is sometimes stated that 75 per cent. of cretinism in goitrous localities is due to goitre in

[1] This account is based on a study of 203 cases of the disease as it is found in Himalayan India. [4.]—R. McC.

the individual. This statement is wholly erroneous. Cretinism is always congenital, whether endemic or sporadic. Cases of thyroid deficiency arising in the individual and due to nutritional, or infectious causes, should be clearly distinguished and designated as "*juvenile myxœdema.*"

Forty-four per cent. of all cretins are goitrous. In a very small percentage of cases (0·5 per cent.) such goitres are congenital, but in the remainder they are acquired subsequent to the onset

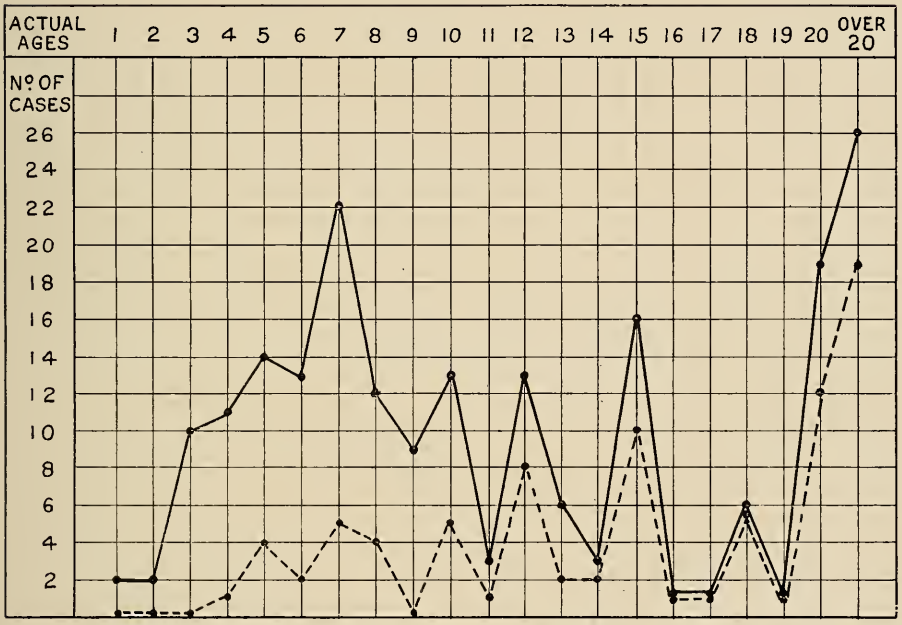


Fig. 55.—Chart showing age-distribution of 203 cretins (unbroken line); also the age-distribution of those among them who had goitre (broken line).

of cretinous symptoms. It is rare to find goitre in a cretin before the third year of life. Seventeen per cent. of all cretins under the age of ten years are goitrous, while no less than seventy per cent. over that age have an accompanying goitre. Thus, cretins are more liable to develop goitre than are healthy children, and their liability to it increases with increasing age (fig. 55). The cretin comes into the world with a thyroid which is either completely fibrosed, and in which goitre cannot arise (fig. 25), or, more commonly, with a thyroid which is in a state of partial

fibrosis and hyperplasia that renders it extremely susceptible to the action of goitrigenous agencies (Figs. 50 and 67). Those portions of the gland which may have escaped complete destruction prior to birth, sooner or later succumb to the post-natal action of these agencies ; the gland becomes goitrous, and rapidly undergoes adenomatous and other degenerative changes, which may wholly deprive it of functional capacity. Hence it is that removal of cretins at as early an age as possible from endemic centres of the disease is a factor of great importance in their successful treatment.

It is sometimes stated that goitrous cretins are, as a rule, less swollen and their condition relatively less grave than those without a goitre. There is little support for such a statement when a large number of cretins are examined. The presence or absence of a goitre makes little or no difference to the child's myxœdematous condition. The mental defect is, however, frequently greater, and nervous symptoms are more commonly present in those with complete fibrosis of the glands, that is to say, in those without a goitre. In such cases the parathyroid glands are also fibrosed, while in the former class they may have escaped to some extent. It is to be remembered that the " goitre " of cretins is in reality made up, in the vast majority of cases, of one or more adenomata in a functionally inactive or imperfectly active organ. The presence of such a goitre would not be beneficial to the child. In some few cases, however, the development of a goitre may be beneficial, and the general myxœdematous condition improve with the development of the thyroid swelling. These cases are very exceptional.

FACTORS WHICH DETERMINE THE DEVELOPMENT OF CRETINISM

The experimental findings detailed in a preceding section afford an adequate explanation of the action of the specific agents of goitre in the production of cretinism. Their action is always ante-natal. There remain, however, to be considered certain other factors which favour the action of these agents. Of these the most important are :

I. The influence of Goitre in the Mother.—In almost every case of endemic cretinism goitre is present in one or both parents; it occurs in about 96 per cent. of the mothers of cretins; in about 40 per cent. of the fathers. While cretinism can arise in the child of a woman free from goitre, it must be established as a rule that maternal goitre—that is to say thyroid impairment—is, in endemic localities, one of the most essential conditions for the development of cretinism in the child.

The maternal goitres in over 80 per cent. of cases are degenerated, the seat of adenomatous or of cystic change. Such an organ cannot be regarded as possessing the same potential powers of functional activity as a normal gland. It may be sufficiently active for the needs of the individual under conditions of slight demand, but its powers of response to excitation are very limited. The investigations of Baumann have shown that a goitre contains less thyroidin than a normal gland per unit of weight, thus demonstrating the functional deficiency of the goitrous organ. But despite this defect the thyroid gland of the majority of goitrous women is, in the absence of other debilitating factors, capable of meeting the additional demands which pregnancy may make upon it. There is, however, a minority in which this is not the case, and it is this minority which constitutes the mothers of cretins.

The experimental production of cretinism in rats affords us some index of this minority; it can be affirmed that about 4 to 5 per cent. of goitrous women will give birth to cretinous children.

The experiments of Halsted, and later of Edmunds, throw an interesting light on the influence of maternal thyroid impairment on the fœtal thyroid, and enable us to understand the train of events which gives rise to cretinism and congenital goitre. Halsted found in the puppies of a bitch from which the thyroid had been removed, and which had been sired by a dog that had also in part been deprived of its thyroid gland, that the thyroid lobes in the puppies were twenty times larger than those of normal puppies. Edmunds repeated this experiment, and obtained a similar result. He found that the changes observed on microscopical examination were those of "compensatory hypertrophy" (hyperplasia), and "were presumably due to an attempt to

compensate for the absence of thyroid in the mother." Our knowledge of the thyroid's function affords an explanation of this phenomenon. One of its functions is to free the body not only of bacterial toxins but of those produced in the ordinary course of metabolism. In the case of the partially thyroidectomized bitch there were more toxins circulating in the blood than her impaired thyroid apparatus could deal with.[1] These toxins, therefore, called forth a response on the part of the puppies' glands, and determined the resultant congenital goitre. Had the bitch been fed on fæcal anaërobic cultures I have no doubt but that some of her puppies would have been cretinous.

Similarly in the goitrous pregnant woman, it is the failure to meet all demands which constitutes a temporary inefficiency of the thyro-parathyroid glands, and places her in a position comparable to that of the partially thyroidectomized bitch of the experiment, but in her case the added action of goitrigenous influences is the final factor determining the destruction of the fœtal gland. Goitrous women frequently exhibit some signs of thyroid insufficiency during pregnancy, of these the most common in goitrous localities is tetany. If they are sub-thyroidic before pregnancy the pregnancy may benefit them, but at the expense of the child's thyroid. Just in so far, then, as the mother's thyroid potentially possesses the inherent power of response to every demand, so far may we expect her child to be born normal, with congenital thyroid instability, with congenital goitre, or with cretinism: all these are to be regarded as but stages in the same process, and the evidence of the minimal, mesial or maximal action of the toxic agents on the unborn child's thyroid apparatus. The following are illustrative cases :—

No. 100.—The mother is myxœdematous (fig. 56). She has a small goitre and suffers from tetany. These attacks are worse during pregnancy; they are more frequent during the spring months, when she may have as many as two or three during one month.

[1] The blood-serum of thyroidectomized dogs is more toxic than normal serum and gives rise to convulsions when injected into healthy dogs (Gley). The urine of such animals also contains a higher percentage of toxic substances than is normal, and thyroid extract administered to them counteracts this toxicity (de Luca and d'Angerio).—R. McC.

There is no unconsciousness during them. She has long been myxœdematous, but believes that she is better than she used to be. She gives a very goitrous and myxœdematous family history. She has had eight children before the present child. They were all, according to her, "born cretins." All were very swollen from birth, and all died before the age of 3. The child shown in the photograph is aged 2. It was remarkably swollen, but improved very decidedly under thyroid feeding.

Nos. 190 and 191.—Family very poor. Mother has a large tumorous goitre and suffers from tetany during pregnancy; she is

Fig. 56.—Myxœdematous mother with her cretinous child.

coarse-skinned and somewhat swollen. Her son, aged 24 (fig. 57), is a typical nervous cretin of an extreme degree; he is a deaf-mute. Her daughter is a typical myxœdematous cretin, aged 18, whose hearing and speech are defective. The mother has had nine children, of whom four are alive; all show signs of cretinism, the two youngest in lesser degree than the two eldest just described. The father has a large tumorous goitre.

No. 82.—Mother has had three perfectly healthy children. She then developed goitre, and subsequently gave birth to the present child, who became a cretin after a convulsive fit when aged 2. This cretin is aged 20 and is very swollen.

The influence of goitre in the male parent is difficult to appraise. It seems likely, however, that it may be of some importance in transmitting a hereditary goitrous taint.

II. Psychic Factors.—Fright, worry, mental depression, and impressions received by the mother during pregnancy have great weight as factors determining the onset of cretinism. There is a reliable history of one or other of these in over 40 per cent. of my cases.

Fig. 57.—A typically " nervous " cretin, aged 24. Height, 3 ft. 6 ins. The right hand is blurred in the illustration owing to spasm.

The following are examples :

No. 142.—A goitrous mother believed herself to have been haunted by a spirit while pregnant with her first child. This child is a cretin and deaf-mute. Her second and third children are alive and healthy.

No. 157.—A goitrous mother lost her first two children, who were healthy, while pregnant with her third child. She (in her own words) " remained always crying and in grief for them." Her third child was " born a cretin " and is a deaf-mute. The next three children are alive and healthy.

No. 177.—The mother is goitrous. The first two children (girls) are alive and healthy. The third child, a son, died during her

fourth pregnancy. The fourth child was " born a cretin " and is a deaf-mute. The fifth child was healthy, but was a girl. The sixth child was a deaf-mute, but not cretinous. The mother's state of " grief at the death of her only son " was considered by her to have caused the cretinism in her fourth child.

No. 175.—The mother is goitrous. The first five children died young, the deaths of several of these occurring during the mother's seventh pregnancy. Her seventh child is a cretin and a deaf-mute. Her sixth child is alive and healthy. She attributed her evil fortune at the death of her children to a " spirit," which preyed greatly upon her mind during her seventh pregnancy. Afterwards " the priest exorcised the spirit." Her eighth child was born normal, and is alive and well.

A history of the baneful influence of " the powers of evil " is very common in Himalayan villages, so much so that one is forced to acknowledge its reality. Other frequent histories are that " while in the jungle with the goats the mother was haunted by a fairy," that she " saw visions," or that she " saw the dead," forms of delusion which, though regarded by the mother as being the causal or exciting factor in producing cretinism in the child, may perhaps be considered as evidence of the defective functional activity of her own thyroid gland. It is known that some cases of delusional insanity are due to this cause and that they may be relieved by thyroid feeding. On the other hand, it is possible that the psychic influences caused the functional depression; certainly such influences place a great strain upon the gland's resources, and they may be the " last straw " which determines its incompetency.

III. **Illnesses in the Mother during Pregnancy.**—These are the determining factors in as large a proportion of cases as 20 per cent. The illnesses most commonly met with are tetany (in itself a sign of thyro-parathyroid defect), rheumatism, rheumatoid arthritis, malaria, and, less commonly, painful eye diseases and abscesses, but any of those mentioned previously (p. 47) may act in this way. The following will serve as illustrative cases :—

No. 177.—A goitrous mother suffered from rheumatism while she was pregnant with her second child. This child is cretinous

to a very severe degree; it is non-goitrous. The first and third children are healthy. The fourth child is dead.

No. 164.—The mother, a goitrous woman, developed severe bronchitis before her sixth child was born. Her first five children are normal. Her sixth is a cretin (fig. 58).

No. 161.—The mother had a severe abscess of the jaw during her third pregnancy. Her first two children are healthy. Her third child is a cretin.

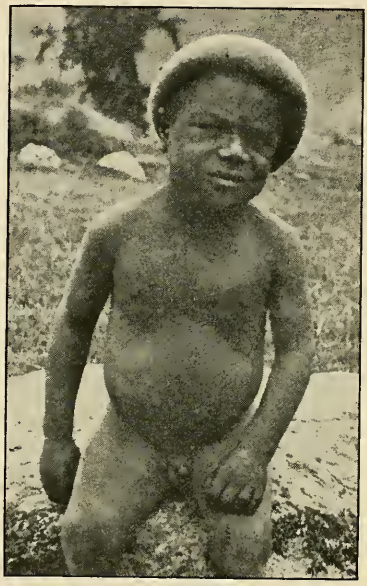


Fig. 58.—Myxœdematous cretin. Aged 24. Height, 3 ft. 6 in.

I believe that illnesses in the mother during pregnancy are of more frequent occurrence than I have noted; it was not until I had collected seventy-eight cases of the disease that a few histories of such illnesses, which had been voluntarily offered, drew my attention to them.

IV. Nutritional Factors.—The influence of these is very great. Their action may be ante-natal or post-natal. The thyroid resources of sub-thyroidic children are often further impaired by malnutrition and by such factors as cold and exposure. Cretinism, especially the nervous type of the disease, is much more common amongst the very poor of endemic areas.

V. **Prolonged or Difficult Labour.**—These may exert a determining influence in a small proportion of cases (10 to 14 per cent.).

Such a history is common in association with other predisposing factors, whether psychic, nutritional or infectious. Its importance is, therefore, difficult to estimate. Since in some cases it may be the only untoward influence present, it may be regarded as a debilitating factor acting on the child directly.

These are the main influences which operate to produce cretinism in the child; they account for about 88 per cent. of all cases in endemic localities. In the remaining 12 per cent., however, the child is not "born a cretin," but is born with a congenital incapacity of the thyroid, so that he may become a cretin later as a result of psychic, nutritional or infectious influences acting on the gland in association with goitrigenous agencies.

Such cases are more properly to be regarded as "juvenile myxœdema," for the development of which congenital thyroid incapacity provides a special tendency.

Sporadic Cretinism.—This form of cretinism differs only from the endemic variety in that it is due to toxic agencies, acting through the maternal blood, other than the specific excitants of endemic goitre. The same predisposing factors are concerned in its production as in endemic cretinism. It occurs in localities where goitre is not endemic, and although cases of the disease may, in rare instances, show an accompanying goitre, its origin is independent of the specific excitant of endemic goitre.

TYPES OF CRETINISM

In endemic districts in the Himalayas there are two distinct types of cretinism apart from the many diverse grades of the affection which are ordinarily met with :

(*a*) *The myxœdematous type*, which corresponds to that form

of the disease met with in Europe and elsewhere (Fig. 58); and

(β) *the nervous type*, which, if it occurs in Europe, was not recognized previous to 1908 as due to thyroid defect (fig. 57).

Cases commonly present the clinical features of a combination of these types.

The symptomatic manifestations of congenital thyroid deficiency are due—

(1) to the inhibition of all developmental processes;

(2) to the depression of all metabolic processes, the diminution of the nutritional exchanges and the impaired elimination of waste products;

(3) to the curtailment of the anti-toxic and protective resources of the body, and the unrestrained action of the products of bacterial growth on the body tissues.

The symptoms of cretinism do not appear, as a rule, until about six months after birth, for reasons which have already been noted; then the failure or retardation of growth usually calls attention to the condition. In endemic localities it is readily recognized, but unless a case has been seen before, sporadic cases may escape recognition until the symptoms are well developed. The following description applies to congenital thyroid defect whether endemic or sporadic; it includes an account (1) of the symptoms resulting from total congenital thyroid deficiency, and (2) of those resulting from minor degrees of such deficiency.

Myxœdematous Type of Cretinism.—Fig. 59 shows a typical cretin of the myxœdematous type. The failure of skeletal growth and the arrest of the process of ossification results in dwarfism and skeletal deformities of various kinds. The bones are short and thick; rachitic curving of the tibia is almost invariable; the epiphyses persist and the fontanelles remain open. The cheek bones are prominent, the root of the nose retracted, the forehead low; the skull varies considerably but is usually larger in proportion than the rest of the skeleton.

Relaxation and infiltration of the ligamentous structures of the body may give rise to knock-knee, flat-foot and varying grades of spinal curvature (fig. 60; compare fig. 34). The infantile condition of the sex organs persists, the failure of their development further depriving the body of the stimulus to physical and mental growth which their functional activity affords. Undescended testicle is common. There is a lack of development

Fig. 59.—Typical cretin. (From a photograph in the possession of the late Sir Victor Horsley, F.R.S.)

of all intellectual and sense functions. Mental torpor is marked; all cretins are idiotic or imbecile in greater or lesser degree; they are commonly deaf-mute or mute, or their powers of hearing and speech are defective; they sleep heavily and are not easily roused. Cutaneous sensibility is impaired and burns and wounds heal badly. The excreta may be passed under them. The muscular system is ill-developed and lacks tone; the head falls forward on the body; the abdomen protrudes, due partly to

muscular relaxation, partly to the disproportionate size of the abdominal organs to the skeleton. Hernias of the umbilicus and other orifices are common. The umbilicus is usually everted (fig. 60). The child supports himself with difficulty—and if it moves at all it crawls about in a sluggish way on its hands and knees, or if it does learn to walk eventually it does so very late.

The depression of the metabolic processes and the impairment

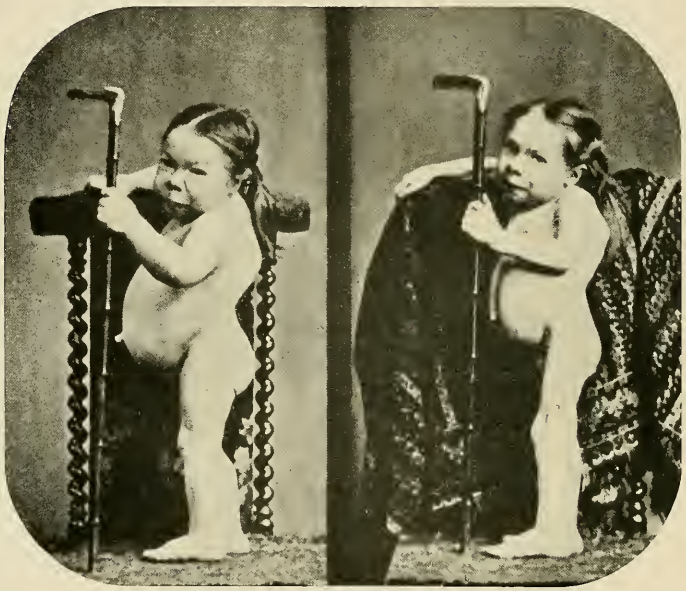


Fig. 60.—Cretin showing marked spinal curvature. Compare with fig. 34. The early effects of treatment are shown in the right-hand figure. (Reproduced by courtesy of Dr. John Thomson.)

of nutrition and elimination lead to the deposit of mucin and fat in all organs and tissues of the body. This deposit occurs chiefly in the subcutaneous tissue. The body swells, supra-clavicular pads of fat appear, the limbs may become thick and stumpy (fig. 59). Sometimes the swelling is chiefly abdominal, and then the limbs may be thin and the skin loose (fig. 60). The nutrition of the skin and its appendages is poor: the skin is harsh and scaly; the hair coarse and ill-grown; the nails imperfectly formed and cracked; the sebaceous and sweat glands

are inactive. The temperature is subnormal. Infiltration of the muscles, ligaments and cartilages increases the muscular weakness and renders movement sluggish; the involuntary and voluntary muscles are alike affected. Constipation is the rule, and is one of the earliest as well as one of the most important signs of all grades of congenital hypothyroidism. The glands of the body are infiltrated and impaired in their action. The tonsils are enlarged; adenoids are present. The tongue is swollen and protrudes from the mouth, from which saliva trickles. The palatine arch is usually high. The face is broad, bloated and expressionless, the cheek bones prominent, the eyelids puffy, the lips thick, the nose flat, the alæ swollen, the forehead low. The eyes lack lustre and are expressionless; the cry is harsh. The hands and feet are small and podgy. Dentition is delayed, and such teeth as do appear are deficient in dentine, ill-formed and decay early. The complexion is muddy or sallow. Infiltration of the neck of the bladder is an early and constant symptom and is the cause of enuresis, which is common in cases of even minor degree. The mucous membranes share in the general infiltration and are especially liable to inflammatory states: conjunctivitis, rhinitis, bronchitis, enteritis, cystitis are all common accompaniments of cretinism.

Finally, cretins are peculiarly susceptible to infectious diseases, to which the large majority succumb in early life.

Minor Congenital Hypothyroidism.—The various grades of cretinism which are so readily recognizable are the grosser evidences of congenital impairment of the thyro-parathyroid glands, but there are many lesser signs and symptoms of congenital hypothyroidism which often escape recognition, the detection of which would be attended with results most beneficial to the backward children who are so afflicted. These, however, can rarely be observed until the end of lactation in breast-fed infants, but from that time onwards such symptoms as the following should at least excite the suspicion that the underlying cause may be a congenital defect of the thyro-parathyroid glands:—

Infantile constipation; unusual coldness of the limbs; failure of the fontanelles to close within the normal period; slowness in learning to balance the head or to sit up; delayed eruption of the teeth and their malformation; early caries of the milk teeth; lack of vivacity and intelligence, and slowness to learn to smile; somnolence; lordosis and scoliosis; slowness to walk; small and weak muscles; mouth breathing and snoring; adenoids and lymphatic enlargements; slowness to talk; rickets; carpo-pedal spasms—tetany; large protuberant abdomen and protruding umbilicus; defects of hearing; enuresis; poor lustre and imperfect growth of hair; undue puffiness; anorexia; and indeed any of the symptoms in minor degree mentioned under cretinism and myxœdema.

It will be recognized that any of these symptoms may be due to causes wholly unconnected with the thyroid gland, and that the existence of one alone need not necessarily indicate defect of this organ, but where several of them co-exist in the same individual they are highly suggestive of such defect and clearly indicate the application of the physiological test of thyroid feeding in small doses. If they are due to thyroid deprivation the beneficial effects of thyroid administration will soon make themselves manifest.

Where, for example, constipation is combined with enuresis and somnolence or other signs of backwardness, it is almost certainly due to thyroid incompetency and is an indication for the use of thyroid medication to tide over the period of the gland's incapacity. If this is not done the constipation will persist, though the enuresis may pass off after the period of the first dentition, and with advancing age it will become more and more pronounced. A state of chronic intestinal stasis will ultimately result, intestinal toxæmia will become extreme and the continued action of these toxins on the thyroid will further depress its functional capacity and lead to various grades of atrophy and to the train of symptoms which results from combined intestinal toxæmia and hypothyroidism. Children of women who are so afflicted may come into the world with thyroids also defective in some degree, and so the whole process

may be repeated in their persons and the stock will tend to become more and more toxæmic, more and more hypothyroidic. I have found this train of events in not a few European children born in the East.

Dr. Leonard Williams has brought forward during the past few years [1] much clinical and therapeutic evidence to support his contention that enlarged tonsils and adenoids in children may be evidences of thyroid insufficiency. His views are deserving of the closest attention, for there is not the slightest doubt in my own mind that the operative removal of these structures is carried at the present day to an undue length. The function of the lymphoid tissues of the throat and naso-pharynx is not definitely known, but there is some experimental evidence which suggests that they yield to the blood a hormone which influences the contractility of involuntary muscles and the blood pressure and possesses also a powerful diuretic action (Ott).[2] It is clear that if the tonsils exercise these functions their removal should not be lightly undertaken. Leonard Williams has summarized his views as follows: "Adenoids and enlarged tonsils occur in children who have an inadequate supply of thyroid secretion. The hypertrophic condition in each case is apparently the result of an endeavour on the part of the organism to supply an internal secretion as nearly allied as possible to the one which is lacking. If the hypertrophy is not very pronounced and if it has not been very long in existence—great enough and protracted enough, that is, to produce complications, such as disease in the tonsils themselves or in the ears—then the exhibition of thyroid extract will cause their regression. It is only when medicinal means have failed that operative interference is justifiable."

One further aspect of hypothyroidism which we must always bear in mind is that toxins have free play to exercise their deleterious action on the various organs and tissues. The central nervous system is peculiarly prone to the attacks of these toxins

[1] *Encyclopædia of Medicine and Surgery*, London, 1912, p. 265.

[2] Ott, I., and Scott, J. C., *Alienist and Neurologist* (St. Louis), 1913, xxxiv, 2; *Proc. Soc. Exp. Biol. and Med.*, New York, 1912–13, x, 47.

so that such conditions as idiopathic epilepsy and certain psychoses should be viewed in this light when a search is being made for their source. Some of the manifold varieties of intestinal toxins may be of high importance in this regard ; so it is that all treatment of sub-thyroidic states should include at the same time anti-toxic and antiseptic treatment of the gastro-intestinal tract.

Before turning to a consideration of the nervous type of cretinism there are certain points with regard to diagnosis which call for brief mention.

Diagnosis.—A diagnosis has to be made between cases of congenital hypothyroidism and Mongolian idiocy, achondroplasia, dwarfism, rickets, congenital adiposity, and hydrocephalus, but a careful consideration of the special features of these conditions, and if necessary the cautious administration of thyroid extract, will rarely leave the physician long in doubt.

SECTION 5

ENDEMIC CRETINISM (continued)

Nervous Cretinism.—This type of the disease has been designated "nervous" for want of a better name, and the term serves at least to call attention to its main features. It may best be described as a condition of cretinous idiocy with associated cerebral diplegia and tetany due to congenital fibrosis of the thyroid and of the parathyroid glands. One-third of all cretins in endemic localities in the Himalayas belong to this type,[1] but both types of the malady may be combined in the same individual.

Cretins of this type, in which the disability is more especially of the central nervous system, in contra-distinction to those of the myxœdematous type, in whom the defect is more especially physical, are usually to be found among the poorest of the people. They are commonly quite helpless, and their bodies invariably bear the scars of burns or other injuries. Their parents frequently do not take the trouble to clothe them, and they are exposed to extremes of heat and cold greater than anything met with in England. Their diet consists only of a daily cake of unleavened bread. The general appearance of such a case is as follows (fig. 57): The skull is elongated, the antero-posterior diameter being long in proportion to the narrow lateral diameter. There is, as a rule, complete deaf-mutism. There may be a knock-kneed spasticity of the lower limbs (fig. 61), or they may be widely separated (fig. 62). The patient exhibits a complete or partial inability to stand upright. When supported on his feet he usually rests on his toes (fig. 57), and the knees may be

[1] Since my original account of "nervous cretinism" was published in 1908 [4], reports of similar cases have appeared from time to time in the literature, indicating that the condition is to be found in England as well as in the Himalayas.—R. McC.

close together or actually crossed, or the lower extremities may remain in a position of rigid extension. There is an increased knee-jerk and there may be marked flexion of the toes on the sole. In those cases in which the cretins are capable of walking there is a peculiar stiffness of gait, and they may walk on their toes; as each foot reaches the ground there is a certain amount of "give" at the knees and ankles, which produces a sort of bobbing motion. There is sometimes flat-foot. The upper limbs

Fig. 61.—"Nervous" cretins with slight myxœdematous symptoms, swelling of face, of the wrists and ankles, and in the armpits. The right-hand figure is that referred to in the text. A section of his thyroid gland is shown in fig. 64.

assume a position of right-angled flexion; the thumb may be drawn into the palm and the fingers closed over it, whilst the wrist is flexed. Spasmodic movements of the upper limbs are common. These are features characteristic of tetany. The spastic rigidity is always worse in the lower limbs. The head may be turned slowly from side to side, and in several of the worst cases I have seen, grimaces occurred. The face is characteristically cretinoid. The degree of swelling varies considerably—it may be marked or slight, and confined to the face, hands, wrists

and ankles. The abdomen is, as a rule, swollen and protuberant. There is always considerable stunting in growth, which may be extreme or relatively slight. The patient's mentality is much disordered ; there appears to be a loss of sensibility in the skin ; puberty is delayed and the sexual organs are ill-developed. A history of convulsive seizures has in a few instances been obtained ; a coarse nystagmus and internal strabismus have been noted in some cases. All degrees of this condition are seen, from a spastic paralysis of the lower limbs to a general rigidity ; in short, the condition is one of cretinous idiocy with associated cerebral

Fig. 62.—Cretin aged 10 years in whom nervous symptoms were very pronounced.

diplegia and tetany. Fig. 57 affords a good illustration of this class of case. The subject is aged 24, is about $3\frac{1}{2}$ ft. in height, is obviously myxœdematous, and presents practically every feature of the type which I have just detailed. His sister is a typical myxœdematous cretin and she is very swollen.

I have sought, in the course of my observations, to find in the histories of these cases some etiological reason for dissociating the obvious cretinoid condition from the no less obvious nervous symptoms. I have not been able to find that cretins of this type are more frequent among the small class in whom the onset of the

cretinism is coincident with some accident or trauma. Nor has a history of prolonged labour, of infectious diseases, of convulsions or of any other affections of childhood afforded any grounds for the dissociation of the nervous from the cretinoid symptoms. The factors which give rise to the nervous symptoms are antenatal in their action; and I believe that this type of the disease, like the myxœdematous, is due to the congenital defect of the thyroid mechanism.

The symptoms which are characteristic of "nervous" cretinism are very similar to those which occur in animals after the complete removal of the thyroid and parathyroid glands. Indeed, as these symptoms are described by Murray, they are

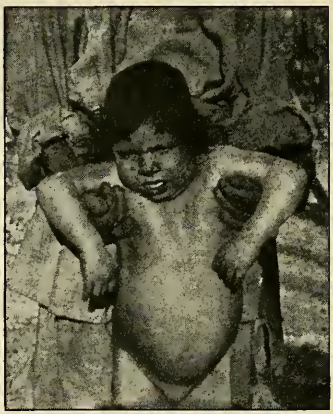


Fig. 63.—Nervous cretinism. Case is of mixed type and shows marked myxœdematous as well as nervous symptoms.

practically identical—a fact which affords some ground for the belief which I have expressed. I have, however, obtained results in three cases by means of the therapeutic test of thyroid feeding, and by detailed post-mortem examination of the glands in a fourth, which to my mind amount to actual proof that the nervous symptoms are due to defect of the whole thyroid apparatus.

Without giving full details of these cases, it may be said that the administration of the fresh and dried extracts of sheep's thyroid produced a striking improvement in the nervous symptoms. The spasm disappeared; in one case (fig. 62) the double internal strabismus, with the associated coarse nystagmus, almost entirely

disappeared. Another—a child (fig. 63) who could only rise to its feet by means of a support, and who could take but a few stumbling paces before its legs gave way—after three months' treatment walked for a distance of over 30 yards without falling. This child was aged 9. It was very much swollen, presented the nervous symptoms in typical degree and, according to its mother, could not speak the simplest word. She affirmed that in consequence of treatment it began to say such simple words as "ma" and "da." There is not the slightest doubt that its hearing very much improved, and the mother found it possible during the last month of treatment to employ it in certain little offices, such as the collecting of bits of wood. The child grew 1 in. in height in three-and-a-half months, while the swelling disappeared and the skin became smooth and soft. The therapeutic test, then, has provided results in these three cases which amply justify my views as to the nature of the condition.

In one case only did I succeed in overcoming the intense prejudice of the people against post-mortem examination. This case is one of very great interest. The disease made its appearance at the end of the first year of life, the factor which determined its manifestation being, it was said, a fall from a low roof. The mother suffered from signs of thyroid insufficiency. The nervous symptoms in the case (fig. 61) were very marked being the most striking feature of the condition. The swelling was slight and limited to the face, wrists, and ankles, with fatty pads in the axilla. There was no marked stunting of growth, and the case might readily have been considered to be one of cerebral diplegia with pronounced mental defect. The naked-eye appearances seen at the post-mortem examination of the child were a slight but uniform enlargement of the thyroid gland. It was very firm to the touch and was not nodular. Parathyroid glands could not be found in spite of the most careful search.

A study of the histological appearances of the thyroid gland in the case revealed the fact that there was a great and uniform increase of the fibrous stroma of the organ (fig. 64). The glandular elements were atrophied and compressed. Typical vesicles were wholly absent and such as were present were almost

completely obliterated. Traces only of inspissated colloid were seen scattered here and there over the sections. The appearances were those of the gland in myxœdema. No trace of parathyroid tissue was found.

Clearly, then, in this case there existed a pronounced defect not only of the thyroid but also of the parathyroid glands. The condition of these organs, when considered in relation to the results obtained by thyroid feeding in three similar cases, affords good ground for the belief that the nervous symptoms were due to their disease.

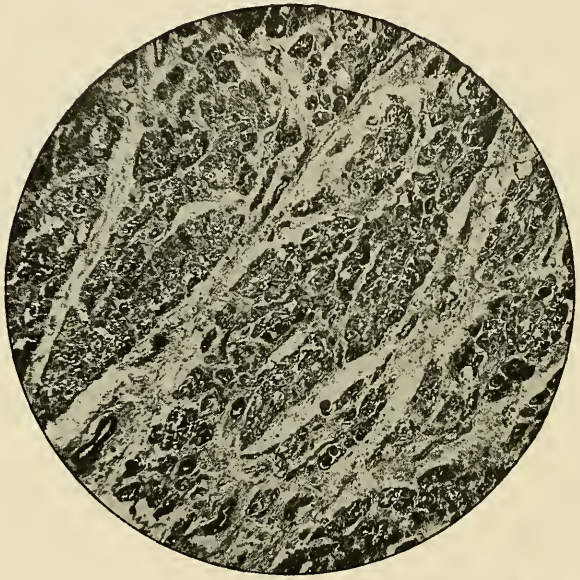


Fig. 64.—Section of thyroid from case of nervous cretinism shown in fig. 61. Note almost complete absence of colloid, great increase of fibrous stroma, loss of vesicular structure and atrophy of parenchyma. × 50.

Further histo-pathological evidence of the dependence of these nervous symptoms on defect of the thyro-parathyroid apparatus is afforded by the work of Edmunds on thyro-parathyroid-ectomized dogs. Pronounced changes occurred in the central nervous system in these animals which he attributed to loss of the parathyroids. In the *spinal cord* the changes are most marked in the medium-sized and smaller cells: "in many of these the (cell) body is partially or wholly destroyed. The Nissl bodies undergo

chromatolysis, the nucleus is destroyed and the cell is invaded by stellate cells. Changes similar to those in the spinal cord are found in all the cells of the *medulla*, though not so marked. In the *cerebellum* the cells of Purkinje show similar appearances to those found in the cord. In the *cerebral cortex* the medium and pyramidal cells exhibit the following changes: "in many the Nissl bodies undergo chromatolysis while many others are utterly destroyed, only the outline of the cell being visible; many of them are invaded by stellate cells. The calcium-content of the brain is reduced by half" (Edmunds).

In view of these post-mortem, therapeutic and experimental findings it may be concluded that the symptoms of this form of cretinism are the outcome of degenerative or developmental defects in the central nervous system, arising in consequence of congenital fibrosis of the whole thyro-parathyroid apparatus.

DEAF-MUTISM AS ASSOCIATED WITH CRETINISM

Eighty-seven per cent. of all cretins are deaf-mutes in greater or lesser degree. In the majority the deaf-mutism is complete; in the minority it is partial. In the nervous type it is almost always complete, less frequently so in the myxœdematous. The defect may be caused in part by the infiltrated condition of the tongue, aural mucosa, Eustachian tubes and naso-pharynx, but it is mainly dependent on imperfect development as well as on infiltration of the higher brain centres and on the lack of receptivity of the nerves.

It is more frequently present in males than in females. In rare cases the condition improves after the development of a goitre.

SECTION 6

TREATMENT OF CONGENITAL HYPOTHYROIDISM AND CRETINISM

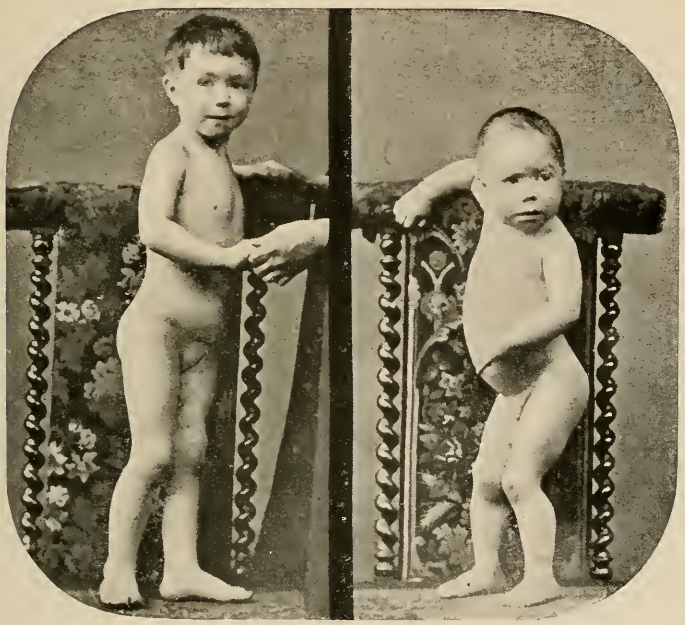
The treatment of this condition is the administration of thyroid substance. For this great therapeutic advance we are indebted to the experimental researches of the late Sir Victor Horsley, and to Dr. George Murray. Its success depends very largely on early diagnosis of the condition and on the extent of the thyroid insufficiency.

Removal from the endemic area is an important measure, no matter what the degree of congenital thyroid impairment may be, but especially so when the impairment is incomplete. In such cases continued subjection to goitrigenous influences will further reduce the functional capacity of such remnants of active thyroid as the child may possess. If, however, cretinoid children are removed from the goitrous area at as early an age as possible the congenitally-impaired thyroid may escape further destruction and regain under thyroid medication a portion of its functional power.

Early diagnosis is essential, since if the specific treatment is long delayed the retardation of mental development is so great that it cannot be brought to a state even remotely approaching to normal. The physical condition, on the other hand, may improve with extraordinary rapidity even when treatment is commenced later. When begun at the earliest possible moment the continued administration of thyroid substance will secure to the child a degree of progress of mental and physical development equal to that of healthy children.

The fresh liquor thyroidei (B.P.) is the best preparation of thyroid substance to employ, but the dried glandular substance,

standardized to contain not less than 0·05 per cent. of iodine, is more convenient and almost equally efficient. The initial dose should be 1 to 2 ♏ of the former or $\frac{1}{4}$ to $\frac{1}{2}$ grain of the latter at bed-time. It is well to combine it for the first fortnight of treatment with grey powder and bicarbonate of soda, the latter drug having the property of aiding it in its action and of promoting normal thyroidal activity. The grey powder secures



After. Before.

FIGS. 65, 66.—Showing the effect of treatment in a case of cretinism. (Reproduced by courtesy of Dr. John Thomson.)

a daily evacuation of the bowel and inhibits intestinal fermentation, in the presence of which thyroid preparations may be rendered uncertain in their action. The dose may be increased gradually by 1 ♏ per week of the liquor or $\frac{1}{2}$ grain of the dried substance. It is rarely necessary to administer more than 5 to 10 ♏ of the liquor or 5 to 7 grains of the powder in a single day.

The immediate effect of the treatment is to cause a loss of weight. This is due to increased oxidation, causing loss of mucin and fat, and to increased excretion of waste products. The skin

becomes moist, the sweat glands begin to act, the bowels become more active, the temperature rises, the pulse quickens, the mental torpor lessens, the child begins to crow and to grow. Later he commences to walk and to talk and pursues an almost normal course of development so long as the treatment is continued (figs. 65, 66).

It is well at first to restrain the child from standing or attempting to walk too soon until the long bones have gained in firmness, otherwise bending of the tibia may occur or become exaggerated.

The treatment should be continued until full maturity is attained, when smaller doses are necessary throughout life in cases of complete atrophy of the gland. In minor cases of thyroid insufficiency in children, however, it may only be necessary to tide over by thyroid feeding a certain period of the gland's incapacity so as to enable it to undergo the regeneration demanded by the body needs: such cases may remain cured without further thyroid treatment.

Signs of excessive dosage are said to evidence themselves by undue increase of the pulse-rate, undue rise of temperature, irritation of the skin, diarrhœa, undue loss of weight, restlessness or actual delirium, or tonic spasms. To these evidences of excessive thyroid feeding the term *thyroidism* has been applied. If faintness occurs the child should be kept in bed, for the heart, like other organs, is infiltrated and takes time to adjust itself to the loss of the infiltrating substances (Hertoghe). Using the thyroid substance in the manner I have indicated, I have rarely observed the ill-effects above referred to.

It is a curious fact that while certain symptoms of subthyroidism are rapidly alleviated by an appropriate dose of thyroid substance, they may be aggravated when it is increased beyond this limit. Enuresis is a case in point—psoriasis is another. Thyroid feeding, again, may give rise to troublesome enuresis in cretins who have not suffered from it previously. Under such circumstances the dose should be reduced to its lowest limit of efficacy.

SECTION 7

PARATHYROID DISEASE AND THE ORIGIN OF TETANY

In the section dealing with myxœdema reference will be found to the histological changes in the brain which are associated with certain cases of sub-thyroidic insanity. These changes are similar to those found by Edmunds in his thyro-parathyroid-ectomized dogs, and which he attributes to loss of the parathyroids. Such degenerative changes are found in cases of insanity where both the thyroid and the parathyroids are involved in the fibrotic process as well as in others where the parathyroids are unaltered. So that ablation or disease of the parathyroid glands is not a necessary factor in their development. Yet there is abundant evidence that the parathyroid glands are intimately concerned with the origin of a certain type of nervous symptom-complex—Tetany—which is obviously the result of irritation of the central nervous system and can be recognized as forming part of the symptoms of nervous cretinism. Parathyroidectomy is often followed by tetany ; but while most animals of carnivorous habits develop this symptom in consequence of the operation, others of the same species, and living under the same conditions of life, may not. In some of these parathyroidectomy leads to a rapidly fatal issue ; in others of the same species it does not. Again in animals of other species the parathyroids may be removed without much risk of tetany. All this has led to great confusion in the interpretation of results, but its explanation is very simple. It is this. Tetany is due to some other factor in addition to the parathyroid insufficiency and this factor is poisoning from the alimentary tract.

No two animals have precisely the same bacterial flora in

the bowel, therefore no two animals of the same species can be expected to react in a precisely similar way when their thyroid glands or their parathyroid glands have been ablated. The bacterial flora of herbivora is wholly different from that of carnivora, and the toxic derivatives of bacterial action in the intestine of these two classes of animals will be widely different in virulence. Of two dogs, for example, one may develop tetany after parathyroidectomy, the other not. The operator in the second, therefore considers that he cannot confirm the findings of the operator in the first; both are right in their observations but both have neglected to take count of the source of the toxic irritants of the central nervous system in cases of tetany—the gastro-intestinal tract. Tetany, as it occurs in the human subject, is almost always, if not invariably, due to gastro-intestinal disorders or to poisons, and my experiments on rats have indicated, I believe, the manner of its origin. When anaërobic cultures from fæces of goitrous subjects, or fæcal filtrate from such persons, are administered throughout pregnancy to goitrous rats, no less than 32 per cent. of their offspring show congenital parathyroid lesions of a definite type. This figure is almost identical with that of cretins showing the nervous symptoms above described (31·9 per cent.). Parathyroid lesions were found only in the offspring of rats which consumed fæcal filtrate or anaërobic cultures. They did not occur amongst the offspring of control rats or of those fed on aërobic cultures from goitrous fæces. The lesions were, therefore, due to the toxins of intestinal anaërobes or to ultra-microscopic forms of these organisms. They were not due to injury at birth, since the offspring of the control rats and of those receiving aërobic cultures were wholly free from them. The lesions were of a constant character and affected the internal (those included in the thyroid) (figs. 67–69), as well as the external parathyroids where these were present.

The changes consisted in engorgement of the vessels of the glandule and of hæmorrhage into it, which destroyed large portions of its substance (figs. 67, 69), and which, had the animals been allowed to survive, would have led to their complete or partial fibrosis. While in all cases of congenital parathyroid disease

observed in rats the thyroid gland was also diseased (hyperplastic) to a greater or lesser extent, it was remarkable that the hæmorrhagic lesions of the parathyroid were constantly observed to be confined within the capsular limits of these glandules.

This experiment, while it indicates how the parathyroid glands may become diseased, does not indicate how the symptoms of

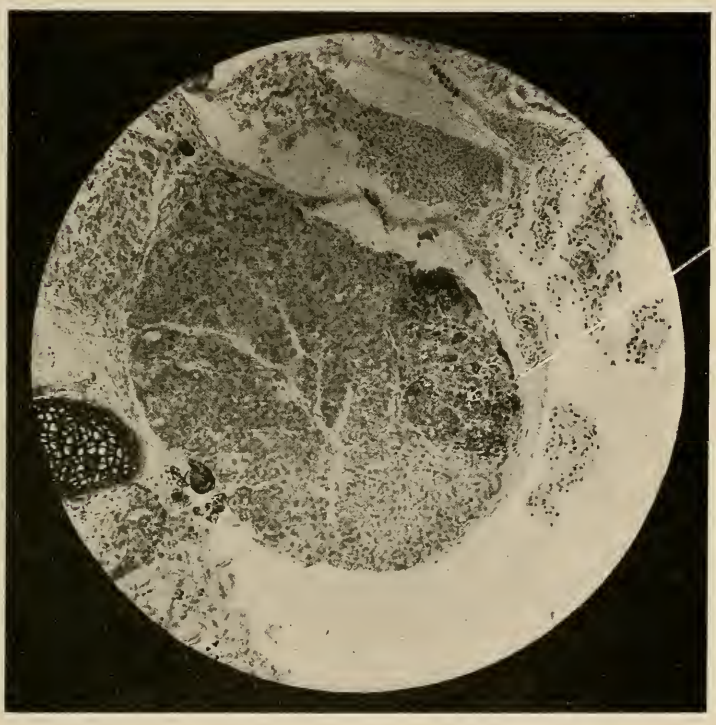


Fig. 67.—Thyroid and parathyroid of 3 to 4-day-old rat. Mother fed on fæcal anaërobes during pregnancy. Thyroid is markedly hyperplastic : lobulated appearance gone, vesicles rare and empty of colloid. Gland invaded by fibroblasts. The parathyroid is the darker, oval area (indicated by the white pointer) embedded in the periphery of the thyroid. It is almost completely destroyed by hæmorrhages into its substance. × 90.

tetany arise. The young rats, during the three to four days they were allowed to live, showed no nervous symptoms of any kind so far as I could detect. Their intestines were probably sterile up to the time of their death and the toxic irritant necessary for the production of the symptoms was, therefore, lacking. Had they been allowed to live they would certainly

have shown tetanoid symptoms sooner or later, for such symptoms are known to be associated with similar parathyroid lesions in children. Escherich found hæmorrhagic lesions of these glands, identical with those I have produced experimentally in rats, in thirty-nine out of an unselected series of eighty-nine infants in his clinic showing nervous symptoms. He noted that the

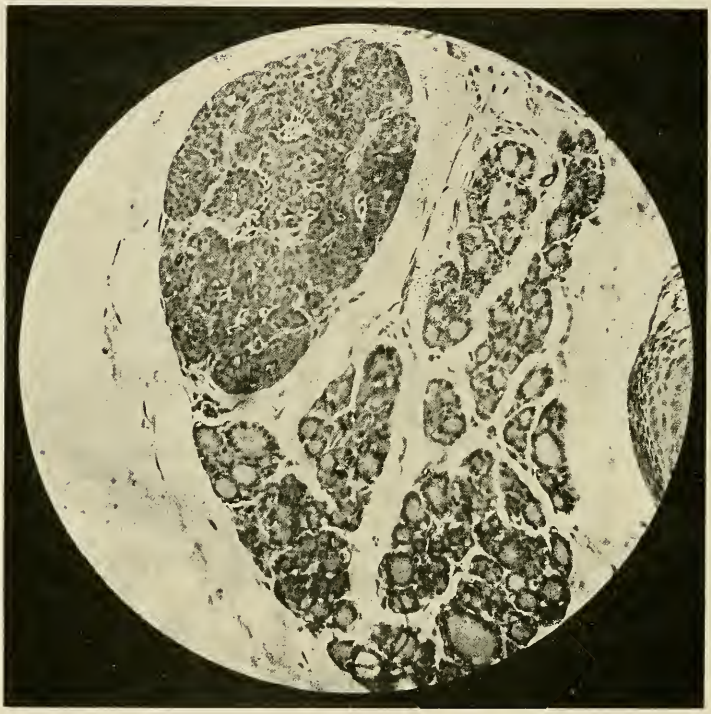


Fig. 68.—Section of normal thyroid and parathyroid gland from a 4-day-old rat. From same case as fig. 49, which shows the normal isthmus. × 180.

severity of the tetanoid symptoms was directly proportional to the severity of the pathological changes in the parathyroids. He attributed the hæmorrhages into the parathyroids to injury at birth, but in the light of my experimental findings in rats these hæmorrhagic lesions are to be attributed not to trauma at birth but to the action on the fœtal glands of the highly virulent products of anaërobic organisms in the maternal intestine.

These findings appear to me to indicate that the factors in the

origin of tetany are (1) a toxic substance which wholly, or more usually partially, destroys the parathyroid and which, as a rule, injures the thyroid at the same time, and (2) a toxic irritant which by its action on the central nervous system gives rise to the symptoms. It is very probable that the same toxic substance which destroys the parathyroid may also act as the irritant of

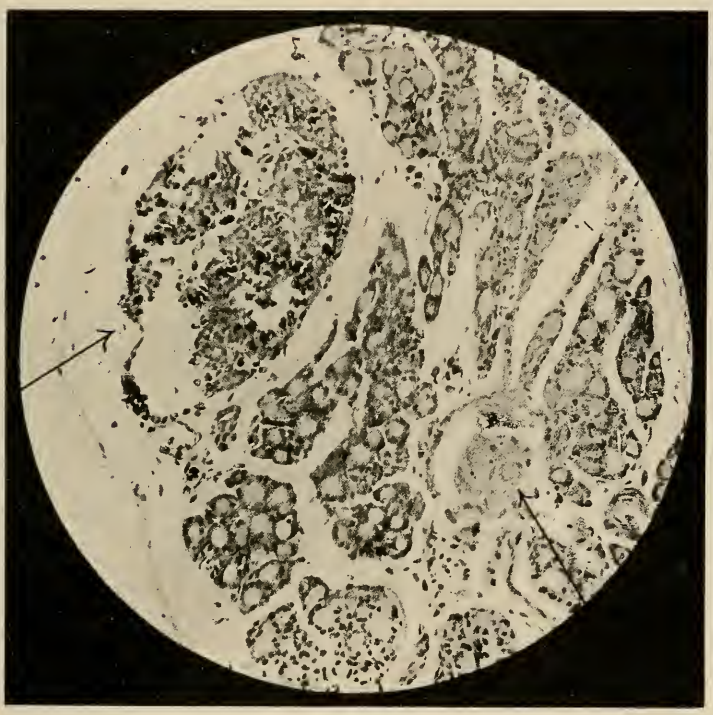


Fig. 69.—Section of thyroid and parathyroid from a 4-day-old rat, showing slight hyperplasia and some fibroblastic invasion in the former. The parathyroid is almost wholly destroyed by hæmorrhage into its substance. From the same case as fig. 50, showing marked hyperplasia and fibrosis of isthmus, the lateral lobes being but slightly involved. × 180.

the central nervous system. It is probable also that the parathyroid lesions are usually congenital and that symptoms of tetany will not arise until an organism has been implanted in the bowel which is capable of producing the essential—and it may be specific—nerve irritant. It is possible also that the parathyroids may in the presence of this specific irritant be relatively

incompetent though not grossly diseased. And it may be that the hypersensitive state of the nerves which disturbance of the calcium metabolism, consequent on thyro-parathyroid incompetency, entails, may render toxins irritative which in health are devoid of any such action. The lesions of the thyro-parathyroid glands will also result in disturbances of metabolism, and in the accumulation in the body of metabolic poisons which by their action on the central nervous system may contribute to the total result, but the primary factor in the genesis of the parathyroid lesion is a poison generated in the gastro-intestinal tract by bacterial action. I think it will be realized when the ætiological and clinical features of tetany have been considered that this conclusion is well founded.

SECTION 8

TETANY

Definition.—Tetany is characterized by bilateral, intermittent and usually painful spasms of the muscles of the extremities and more rarely of other parts of the body, and by heightened excitability of the nervous system.

Ætiology.—In the preceding section the origin of the nervous symptoms was discussed, and referred to congenital thyro-parathyroid defect consequent on the action of the toxic products of maternal anaërobic micro-organisms on the fœtal thyro-parathyroid apparatus in general and on the parathyroid glands in particular. Under certain circumstances, then, children may be born into the world with congenital parathyroid instability or with actual impairment of the gland's function in consequence of hæmorrhage and fibrosis. Such children will throughout life be susceptible to the action of toxic agents which in the normal individual would exercise no effect.

But while the pathological state which results in tetany may often be congenital it is also frequently acquired and, in this case, the same factors which determine all departures of the thyroid apparatus from normal operate in its production: *e.g.* nervous, nutritional and toxic (including infections).

Thus, tetany may occur:

(1) During the course of pregnancy and lactation. (The tetany of nursing women—Trousseau.)

(2) In the course of, or following, acute infectious diseases, particularly those of childhood—scarlatina, measles, tuberculosis, influenza, acute articular rheumatism, pneumonia; and in intestinal and other alimentary tract infections—typhoid, cholera, diarrhœa.

(3) In the course of nutritional disturbances, especially in childhood—rickets, osteomalacia; or in gastric and intestinal disorders—gastric or intestinal dilatation and stagnation. (Tetany of infants, gastric tetany.)

(4) In toxæmias of intestinal origin—anaërobic and other infections of the bowel, helminthiasis.

(5) As a result of poisoning by lead, ergotin, morphine, phosphorus, alcohol, chloroform, carbonic acid, or the poisons of uræmia.

(6) In the course of goitre, cretinism, Graves' disease and myxœdema; and under the influence of certain psychic factors in those predisposed to it.

(7) In the course of some nervous diseases: cerebral tumour, syringomyelia, cysts of the cerebellum and epilepsy.

All these factors will be more likely to produce the symptom-complex of tetany in those in whom there is a congenital instability or actual injury of the parathyroid glands.

Tetany may occur as sporadic cases or in epidemic form, and is endemic in certain localities. Its ætiological features may be illustrated by a consideration of the malady as it occurs in endemic form.

ENDEMIC TETANY [11]

Endemic tetany occurs in such large cities as Vienna and Heidelberg, where it is known as idiopathic or occupation tetany. The endemic tetany of cities possesses very definite characters: it has a marked relationship to the time of year, being most frequently observed in the spring months; it has a tendency to assume epidemic proportions; it is very local in its distribution; and it shows a marked tendency to affect persons employed in certain trades—shoemakers, tailors, carpenters, and locksmiths.

It occurs also in certain goitrous districts in the Himalayas, where it is well recognized by the inhabitants, whose term "hatti fallategen" ("a turning in of the hands") admirably describes it. Its distribution in these areas is peculiarly local, and appears

to correspond with the distribution of goitre. Chvostek states that tetany is rare in regions where goitre is endemic, but this is not my experience in the Himalayas, the reverse being the case. It is met with most commonly in localities where the endemicity of goitre is highest, and does not appear to prevail in parts of the country where goitre is not found. In the district of Hunza, which is peculiar in that goitre is unknown there, tetany does not occur. In Barmis, also, and in the Ishkomin valley, no cases of the disease have been met with; in both of these places goitre either does not occur or its endemicity is very slight.

Sufferers from tetany appear to be able to rid themselves of it by going to a locality where it does not prevail; the same is true of goitre in its early stages. Thus, a young married woman had suffered from the disease during two successive springs while living in Gilgit. She then went to reside in Ishkomin, where she lived for three years; while there she was free from tetany, although she was pregnant and suckled her child during this period. On her return to Gilgit she again developed the malady.

In Himalayan districts tetany is a disease of women; it is very rarely found in the male. The condition also affects women at a very definite period of their lives—the child-bearing period. Girls under the age of 14 do not appear to suffer. It is almost entirely confined to married women between the ages of 15 and 42. It is most common between the ages of 20 and 30 years. The disease usually makes its first appearance between the ages of 15 and 30 years. It is rare to find that it commences after the age of 30. In these features tetany presents a close analogy to Graves' disease.

There is a marked family tendency to tetany; when a daughter suffers, her mother, and possibly her grandmother, has suffered before her. Sisters also are frequently affected. This tendency is due to congenital predisposition to the malady.

The children of women who suffer from tetany are frequently cretinous. About 25 per cent. of women so afflicted give birth

to cretins. Tetany in the mother is, therefore, a signal of great danger to the child.

Menstruation increases the frequency and the severity of the attacks of tetany, especially so when this function is in any way disordered. The loss of calcium with the menstrual flow, and the thyro-parathyroid's function of regulating calcium metabolism afford an explanation of the increased irritability of the nervous system at this period.

The association of tetany with pregnancy and lactation is one of its most striking characteristics. It commonly develops during pregnancy, more commonly during the second than the first. Sometimes the onset is during lactation. Attacks are always worse should the patient be pregnant or suckling a child. Tetany also arises most frequently, and the attacks are most severe during the later months of pregnancy or the earlier months of lactation. Some women suffer more during pregnancy than during lactation ; in others the reverse is true. Attacks of tetany cease, as a rule, when child-bearing ceases.

The seasonal prevalence of endemic tetany—its limitation to the spring months, except in rare instances—is its most distinctive feature. It begins to manifest itself about the middle of February and prevails until about the end of May. With the rise of atmospheric temperature after this month the disease ceases abruptly. Cases are unknown to develop during the summer months when the temperature in the shade may reach 100° F. The disease may arise during the autumn and winter months in association with pregnancy or lactation, but this is rare. The attacks are then milder and the intervals between them longer. During the spring months the disease is so common in these regions that it may be said to be *epidemic*. A woman who has suffered from the malady during one spring is practically certain to suffer during succeeding springs. It may recur every spring for as long a period as eighteen years. Rarely does it cease spontaneously during the child-bearing period.

Certain factors are capable of inducing spasms in those liable to tetany. Amongst the most important of these is the "chill" which results from the sudden lowering of the atmospheric

temperature by rain during the spring in these regions. Fright and mental distress have the same effect, as also have attacks of acute illnesses. The drinking of cold water often provides the stimulus which induces the spasms.

In all cases of tetany studied by me in this region the patients have been goitrous with one exception, and this was the only male case in the series. The goitre was always degenerated, the seat of adenomatous or cystic changes. The functional impairment of the thyroid apparatus which results from goitre appears to be of great importance in the genesis of tetany. The two maladies have a like distribution in Himalayan regions, both have the same seasonal prevalence, and both can be cured by the same remedies. It is the accumulation of demand on the impaired thyro-parathyroid resources which, in the presence of pregnancy and lactation, and of the specific intestinal toxin, determines the onset of symptoms. Some observers have thought that goitre may produce them by pressing on the parathyroids. It is not necessary to assume that goitre acts in this way; tetany would be more common in men in these regions if it did. The specific action of the toxic products of certain intestinal anaërobes on the thyro-parathyroid glands and on the nerve tissues is the true cause, pregnancy and lactation account for its more common occurrence in women.

Rheumatism, malaria, intestinal disorders, helminthiasis, are frequently associated with tetany. Their influence in favouring its development is obvious. Symptoms of incomplete myxœdema are present in about 8 per cent. of women who suffer from tetany.

To account for the occurrence of tetany in persons employed in certain trades, such as shoemakers, tailors, locksmiths, etc., it is suggested that these are all trades which admit of ready infection of the intestinal tract by organisms from the soil. The continued ingestion of such organisms may, especially in the presence of abnormal states of the gastro-intestinal tract, lead to the implantation of organisms whose toxins possess specific tetanic properties. The effect of the spore-bearing organism in producing tetanic spasms in dogs will be remembered in this

connection as well as the fact that the organism was obtained from the fæces of a goitrous horse.

Symptoms.—The spasms are symmetrical. The fingers are semi-flexed at the metacarpo-phalangeal joints and fully extended at the inter-phalangeal joints. The three fingers are adducted towards the middle finger and the thumb is contracted in the palm giving rise to the appearance known as "accoucheur's hand." The wrist is flexed and adducted towards the ulnar side, the elbows are bent and the arms folded over the chest. The feet are arched and turned inwards, the toes are drawn together, flexed and inwardly rotated. The ankles and knees are extended. The affection may be limited to the hands and feet giving rise to the so-called "carpo-pedal spasm" which is so commonly seen in the case of gastro-intestinal disorders and rickets in children.

In severe cases the cramps may extend to the muscles of the trunk, neck, face and larynx; the respiratory and intercostal muscles may be involved, as may also be the diaphragm, giving rise to dyspnœa and cyanosis. Laryngeal spasm is peculiarly liable to occur in the tetany of children. The spasms of the body muscles may cause the whole body to be extended. Fibrillary twitchings of the muscles of the face may occur. Trismus is rare.

The rigid muscles are tender; the reflexes are usually unaltered; there is no loss of consciousness during an attack. After an attack complaints may be made of pains in the bones and joints.

According to Falta the involuntary muscles are affected also in these spasms; spasmodic contraction of the stomach and various parts of the intestinal tract have been demonstrated by X-ray examination. Spasm of the bladder sphincter has been reported in isolated cases, especially in the tetany of infants, leading to retention of urine.

Complaints may be made by sufferers of sensations of tension in the feet and hands, while patients are abnormally sensitive to thermal stimuli, spasms being produced by the application

of heat or more especially of cold—as when drinking a draught of cold water.

The metabolic disturbances in tetany are ill-understood; many of those which have been described are probably due to associated thyroid disorder. The most important is the disturbance of the calcium metabolism and the withdrawal of this substance from the nerve tissues leading to their heightened excitability (MacCallum and Edmunds). Certain changes in the teeth have been described but their dependence on the parathyroid lesion is based on the slenderest of foundations, namely, on the observed results of parathyroidectomy in rats—a wholly impossible operation without grave injury to the thyroid.

Tetany may lead to convulsions in children, and seizures resembling epilepsy may occasionally be associated with it in adults. Indeed Bolton [1] goes so far as to attribute idiopathic epilepsy to the action of chronic alimentary auto-intoxication consequent on defective function of the thyroid and parathyroid glands. He considers that the rectal administration of fresh extracts of the thyroid and parathyroid glands will cure such cases.

The signs of increased excitability of the nervous system during the intervals between attacks of tetany are: Trousseau's sign—the production of spasms by compression of the nerves or blood vessels of the part. Erb's sign—the hyper-excitability of the nerves to electrical currents; and Chvostek's sign of the production of facial spasm by tapping either the facial muscles or the facial nerve.

In endemic areas tetany varies in severity: the majority of cases are mild, the spasms being frequently limited to the upper limbs, more rarely they affect the lower limbs also. In the minority the attacks are of greater severity and involve a wider range of muscles. Fever of a mild type is present in about 55 per cent. of cases during an attack; sweating occurs in 33 per cent. The attacks manifest a more or less marked periodicity. First attacks are most commonly of a daily type, the spasms coming on in the evening and lasting one, two or three hours. In cases of longer standing the attacks may come on every other

[1] *Novo. Icon. d. l. Salpêt*, 1914, Sept.–Dec., p. 360.

day, or after an interval of two or three days. In others the attacks are spread over a period of three or four days or even longer, during which time the spasms may be intermittent or more or less continuous. The period of spasm is then followed by a tetany-free interval lasting several days.

Diagnosis of Tetany.—A diagnosis has to be made from tetanus, strychnine-poisoning, hysteria and ergot-poisoning. In tetanus the "accoucheur's hand" is absent, the spasms begin in the head and neck; trismus is an early symptom. In strychnine-poisoning the spasms are clonic rather than tetanic and affect the whole body. In hysteria the contractures are usually unilateral and Trousseau's and Erb's signs are absent while other hysterical manifestations are present. Ergot-poisoning may closely simulate it and is difficult to exclude except by microscopical examination of the food and fæces for the fungus. In connection with the close resemblance of ergotin-poisoning to tetany, to which attention was first drawn by A. Fuchs, it is interesting to recall Biedl's statement that an amino-base (imidoazolyethylamin) is formed in the putrefaction of histidin, which is identical with the active agent in ergotin. It is some such agent, resulting from the growth of intestinal anaërobes, which causes tetany.

Treatment of Tetany.—In tetany, due to whatever cause, it is the condition causing it which requires treatment. In mild cases in girls about puberty and in endemic areas where the disease may be associated with goitre it is necessary to treat the underlying intestinal toxæmia by appropriate diet, purgation—preferably by calomel—and intestinal antiseptics, thymol, beta- or benzo-naphthol. In such cases also thyroid extract will prove of benefit. Thyroid substance is more efficacious in the treatment of this disease than parathyroid substance alone. Although rare cases have been reported in which the administration of the latter was efficacious, as a rule it stands in marked contrast to thyroid substance, which so readily benefits thyroid inadequacy, being without any constant beneficial effect in parathyroid insufficiency.

The administration of soluble salts of calcium, especially the lactate, is of value in cutting short the attacks although the salts are not curative.

The introduction of acids into animals suffering from post-operative tetany also relieves the symptoms (Wilson, Stearns and Jannery). This has led to the assumption that they may be in part an expression of alkalosis as much as an expression of loss of calcium. The administration of acids may, therefore, prove of benefit in view of this finding. The question, however, is still in the experimental stage.

In children the underlying cause is almost always rickets or gastro-intestinal disorders. These require appropriate treatment, thyroid medication being indicated in the former. In some cases in infants the condition is due to gastric dilatation and stagnation of the stomach contents or to dilatation of the colon. In such cases the disease is often fatal. Lavage of the stomach or colon, as the case may be, with appropriate diet—peptonized milk, citrated milk, albumin water—and intestinal antiseptics may relieve the condition, but if these fail resort should be had to operative correction of the stagnation.

Diet is of great importance in the treatment of tetany. Meat aggravates the symptoms and should not be given, while milk, which is rich in calcium, tends to prevent its recurrence. In the tetany of children indican, according to Mutch, is present in large amounts in the urine and its appearance and disappearance seems to correspond with the appearance and disappearance of the tetany. The spasms can be induced or controlled by increasing or decreasing the proteid in the food.

SECTION 9

INFLAMMATIONS AND SIMPLE TOXÆMIC GOITRE

The second group of diseases with which we have to deal include inflammations of the thyroid and its hyperplasias, due to other than endemic influences.

INFLAMMATION OF THE THYROID GLAND

In the second part of this work the various conditions which may give rise to acute and chronic inflammations of the thyroid have been dealt with at length. Attention has also been directed to the comparative frequency with which inflammations occur in such conditions as acute tonsillitis, acute articular rheumatism, and secondary syphilis. It does not appear necessary to consider in detail the clinical manifestations of inflammation of this gland, which are those of inflammation in any other part of the body. As a rule it leads, when acute, to suppuration, which can usually be detected by fluctuation in the tender swollen area which is limited by the outline of the gland. The skin over the area may or may not be reddened. In more chronic cases, as in those which may occur after typhoid fever, the abscess may be hard to distinguish from a cyst of the gland. As fluctuation is always difficult to appreciate owing to the layers of muscles covering the organ, two signs to which attention has been directed by Lahey, may prove of diagnostic value, viz. (1) the limitation of the chin elevation, and (2) the depression of the chin on the sternum when swallowing. Both are due to the pressure of the sterno-hyoid, sterno-thyroid and omo-hyoid muscles on the abscess covered by them. Elevation of the chin causes pain owing to the pressure of the stretched muscles on the abscess. The contraction of these muscles during deglutition similarly

causes pain, which is lessened by the depression of the chin on the chest.

The treatment of abscess is incision, under local anæsthesia, and drainage. The incision should be made after careful dissection down to the gland. Lahey advises that the fibres of the sterno-hyoid be cut transversely on either side of the median incision, as otherwise the longitudinal tension of the sterno-hyoid and sterno-thyroid produces a tendency for the edges of the incision to come together, thus interfering with drainage.

The influence of thyroiditis in causing various degrees of thyroid deficiency has already been referred to in an earlier part of the work.

The diseases due to hyperplasias, which are not traceable to endemic influences, may be *congenital* or *acquired.*

Included in the congenital class are :

1. Congenital myxœdema (sporadic cretinism), and various grades of hypothyroidism.
2. Parathyroid disease—tetany.

These have already been sufficiently dealt with in the preceding sections.

In the acquired class are :

1. Simple toxæmic goitre.
2. Infantile and juvenile forms of myxœdema and various grades of hypothyroidism.
3. Myxœdema of adults and various grades of adult hypothyroidism.
4. Infantile and adult forms of tetany.
5. Graves' disease.

SIMPLE TOXÆMIC GOITRE

It cannot fail to have struck most medical men, especially those practising in large towns, that thyroid swelling is comparatively common at the present time amongst young women even in areas where goitre is not generally supposed to be endemic. The modern low-necked frock which is worn by day has drawn

attention to its frequency. In a walk through the streets of London, for example, one meets with such cases by the score, while they seem to be as common amongst the upper as amongst the poorer classes.

We might look upon these cases as evidence of a low endemicity of goitre in places where its occurrence has not hitherto been suspected, but there are good grounds for relegating such goitres to a class by themselves. They are usually uniform swellings of a small size, and might be considered to be physiological did not one realize that underlying them all is some toxæmic cause. The same nutritional, psychic and infectious factors determine their production as in endemic goitre, but they differ from this form of thyroid enlargement in that they do not progress to the same size, nor undergo the same degree of degenerative, adenomatous or cystic change. They differ also ætiologically in that in all probability they are due to the action of toxic products of organisms other than the specific agencies of endemic goitre, such, for example, as the *B. coli communis*.

They develop chiefly at the onset of menstruation in sallow, chlorotic and constipated girls, and are due almost invariably to intestinal toxæmia following on chronic constipation and intestinal stasis. A "controlling appendix," that is to say an appendix which by its adhesion to neighbouring parts is controlling the onward flow of the ileal contents into the large bowel and producing ileal stasis, may be associated with such goitre as in the cases previously referred to (page 53).

Hence I have designated them "toxæmic goitre" to indicate their ætiological causation, and to distinguish them from the goitre of endemic areas, with which, however, they are closely analogous in their origin.

It is to be remembered that toxæmic goitre in the mother is of great importance in determining the production of congenital thyroid instability in the child. The symptoms of Graves' disease also may be superimposed upon toxæmic goitre.

The treatment of these cases is that already laid down for endemic goitre in its early stages, and may be summed up as attention to the bowels, proper dietary, thyroid extract and

intestinal antiseptics. One not uncommonly meets with cases in girls in which severe headache and profuse and painful menstruation is associated with a small goitre which increases in size at these periods. Such cases are greatly benefited by thyroid therapy and by attention to the bowels.

The X-ray examination of the intestinal tract and the removal, where these are found, of such abnormalities as may be the cause of stasis—controlling appendix and bands—are obviously indicated in cases of toxæmic goitre. Vaccines, similar to those employed in the treatment of endemic goitre, may be used with advantage in this condition. They appear to benefit not only the thyroid enlargement but the intestinal toxæmia to which it is due.

SECTION 10

MYXŒDEMA

The forms of disease due to acquired thyroidal defect are: Infantile myxœdema, juvenile myxœdema, and the myxœdema of adults. The defect in all these is due to the same causes, and its manifestations vary only with the period of onset.

Thus, in cases arising before the first year of life, the clinical picture is one of cretinism (the term "cretinism" should, however, be restricted to cases of *congenital* thyroid deficiency). After the first year of life, when ossification has proceeded to the extent of closure of the fontanelles, the case is only distinguishable from one of cretinism by this fact. It is then called "Infantile myxœdema."

Arising later in the developmental period the clinical picture is one of myxœdema to which is superadded a cessation of ossification and growth proportionate to the amount of incomplete bone in the body at the time of onset of the thyroidal incapacity. With the age of puberty the sex organs either fail to develop, with all the consequences to growth and mental development which this failure entails, or their development is retarded in proportion to the degree of suppression of the thyroid's function. The condition under these circumstances is known as "juvenile myxœdema."

Synonyms.—Athyrosis; hypothyrosis; hypothyroidism; sub-thyroidism; cachexia strumipriva; cachexia thyreopriva.

Definition.—A condition of cachexia, resulting from loss or impairment of function of the thyroid gland, and characterized by the depression of all vital processes, mental failure and trophic

disturbances of the skin and subcutaneous tissues. Its manifestations are proportionate to the degree of thyroidal impairment and to the age of the subject.

The condition was first recognized by Gull in 1873, and the term "myxœdema" was applied to it by Ord in 1878. Its connection with the thyroid gland was shown by the brothers Reverdin in 1882 and later by Kocher, who noted the cachectic symptoms which resulted from total extirpation of the thyroid in cases of goitre. To these symptoms Kocher gave the name "Cachexia strumipriva." In this country the experimental work of the late Sir Victor Horsley added greatly to our knowledge of the condition, and indicated the means of its treatment by thyroid substitution therapy.

Prevalence.—The complete syndrome of myxœdema is of comparatively rare occurrence, but the manifestations of the gland's partial impairment of function are frequent. Typical myxœdema is no more common in localities where goitre is endemic than in other areas. Goitre rarely gives rise to myxœdema in the individual, although some degree of thyroid impairment is common in persons who are the subjects of goitre of long standing which is the seat of extensive degenerative change.

There is a marked hereditary tendency or family predisposition to the disease. Sub-thyroidism in the mother is a common cause of sub-thyroidism in the child, as has been explained when dealing with the genesis of endemic cretinism. Indeed, in all cases of backwardness in children the mothers should be carefully examined from this point of view.

Myxœdema is more common in cold than hot climates.

Ætiology.—In contrast to endemic cretinism, which is more common in males, myxœdema is more common in females. Eighty per cent. of all cases occur in women (Biedl). It develops in the adult usually during the period of sexual activity, and many cases make their appearance in women about the time of the climacteric. In many such women the stimulus of pregnancy has masked the thyroidal defect, which becomes obvious on its

withdrawal. Multiparæ are more prone to the disease than other women; rapid child-bearing and the accidents peculiar to the sexual life of women may be regarded as factors which hasten or determine its onset.

The ætiological factors in its production are those which determine all departures of the thyroid apparatus from normal: malnutrition, or excessive indulgence in such articles as meat and alcohol, psychic factors, fright, worry, anxiety and the shock of trauma, are the predisposing causes of the disease; these factors, aiding as they do the action of toxic agencies, may so depress the thyroid's function as to cause symptoms of minor thyroid insufficiency. The complete syndrome of myxœdema, however, is due to a process of acute or chronic inflammation arising during the course of infectious diseases or to the overwhelming action of toxic agencies. Chronic intoxications are a frequent cause of the gland's partial atrophy and cirrhosis. The mode of operation of these agencies has already been fully discussed; it will suffice here to indicate the importance of Graves' disease, of syphilis, hereditary or acquired, of the infectious diseases of childhood, and above all of chronic intestinal toxæmia in the genesis of thyroid insufficiency.

Sub-thyroidic states are especially prone to arise in all those who have inherited an instability or incapacity of the thyroid apparatus, for this reason the family history should be carefully searched for evidences of sub-thyroidic taint.

THE THYROID, PARATHYROID AND PITUITARY GLANDS IN MYXŒDEMA

The Thyroid Gland.—The histological changes which occur in the thyroid in their course from hyperplasia to fibrosis, and the nutritional and other factors which determine variations in the picture, have been fully discussed in an earlier part of this book.

These changes result in all cases in greater or lesser degrees of atrophy and fibrosis (figs. 24, 70), so that as a rule the gland is diminished in size or may be wholly atrophied. It is pale yellowish-white in colour and is firm in consistency. Its fibrous

tissue may be swollen and infiltrated and it may be invaded by lymphocytes. These cells may be very numerous and lie in clumps or surround existing vesicles (Kojima). Their presence is limited to certain cases only in whom a definite group of mental symptoms may be present (*vide infra*). Similar lymphocytic infiltration may occur in the atrophic thyroids resulting from Graves' disease.

The severity of the symptoms cannot be gauged by the size of the gland ; these depend solely on the degree of parenchyma destruction and of deficiency of secretion. In some extreme

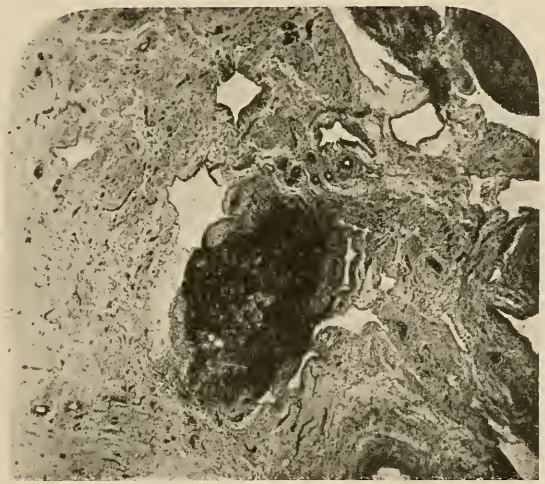


Fig. 70.—Section of thyroid from an old case of myxœdema showing its complete conversion into fibrous tissue. (From a specimen in the possession of the late Sir Victor Horsley, F.R.S.)

cases the organ is converted into a mass of fibrous tissue (fig. 70) ; in others which are less severe some variable amount of parenchyma tissue and vesicles may be found. In the myxœdema of adults the thyroid's function is rarely wholly suppressed, but is so diminished as to bring about the infiltration of the tissues which is characteristic of this condition.

Parathyroid Glands.—It is uncertain to what extent these are involved in the process which gives rise to myxœdema, but the

fact that tetany is a frequent manifestation in goitrous women in the Himalayas who are the subjects of partial myxœdema, and that many cretins show signs of extensive involvement of the central nervous system which are referable at least in part to lesions of the parathyroids, indicate that in myxœdema they do not always escape involvement. Fig. 71 shows the fibrotic remains of the parathyroid in a case of long standing. The section is from the collection of specimens belonging to the late Sir Victor Horsley.

Forsyth has reported a case of myxœdema in a woman of

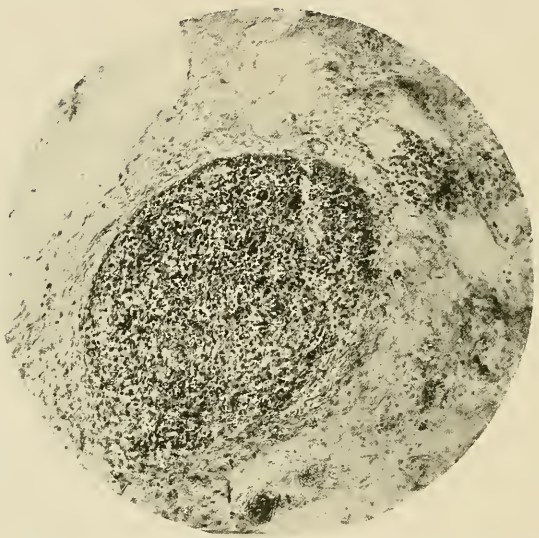


Fig. 71.—Remains of the parathyroid from a case of myxœdema. Pronounced atrophy of parenchyma cells and great increase of fibrous tissue. (From a specimen in the possession of the late Sir Victor Horsley, F.R.S.)

forty-eight in whom, in addition to vesicle and colloid formation, there was an abnormal increase in the connective tissue of the parathyroids and a thickening of their artery walls.

Changes in the parathyroid glands have also been described in four cases of myxœdema by Kojima, in two of which there were evidences of what he considers to be hyperaction in the shape of vesicle and colloid formation. Of two others the parathyroids were necrotic in one; in the other the left parathyroid was lessened in functional capacity by coagulation necrosis, while

the right showed the above-mentioned evidences of increased functional action.[1]

Mott also has recorded a similar instance of so-called " substitutive increase in colloid " in the parathyroids from a case of hypothyroidism.

There is thus considerable evidence to show that the parathyroids may be involved in myxœdema, as in cretinism, in such a way as to impair their function. They are, however, not always involved (*vide infra*), and it is interesting to note that, even when they are not, changes may occur in the nervous system similar to those demonstrated by Edmunds in thyro-parathyroidectomized dogs, showing that these changes are not necessarily dependent on loss of function of the parathyroids.

The involvement of the parathyroids probably depends on the nature and mode of action of the causal agent of the thyroid defect. When acting locally in the thyroid itself as in chronic inflammatory states, the parathyroids may escape; when, on the other hand, the agent is an intestinal toxin circulating in the blood they are likely to suffer.

The Pituitary Body.—We have seen that this organ may undergo enlargement to the extent of two or three times its normal size in thyroidless animals; the increase is largely one of the *pars intermedia*, the cells of which structure invade the *pars nervosa* (Herring). It has been shown by Mott and Brun that it may enlarge in myxœdema also, that its weight may be increased and that it may show a greatly increased colloid-content. Mott has also found the same invasion of the *pars nervosa* by the cells of the *pars intermedia* in certain cases of sub-thyroidic insanity.

This enlargement is thought by some to represent an attempt at compensation for the thyroid's insufficiency. It appears to me that the changes in the pituitary are due more likely to the

[1] It cannot be admitted as proven that the presence of colloid in the parathyroids or even in the pituitary gland in cases of thyroid suppression is evidence of an attempt to compensate for the loss of thyroid function; this might as readily indicate hypo-function of these organs. Since thyroid suppression signifies loss of thyroid secretion, iodine-containing colloid would not be likely to accumulate in either of these organs if they were acting for the thyroid.—R. McC.

same toxic or other agencies which determined the thyroid's fibrosis or to the unrestrained action of these agencies which the thyroid's incompetency renders possible. The pituitary body is not invariably enlarged in myxœdema.

MORBID ANATOMY AMD SYMPTOMATOLOGY

The morbid anatomical changes which occur in the various organs and tissues of the body in consequence of the withdrawal of the thyroid's secretion are the result—

(1) of faulty nutrition of all cells, and

(2) of the infiltration of cells and tissues by the products of imperfect katabolism. Included in these changes is the resultant depression of the body's antitoxic and protective resources, whereby the unrestrained action of divers toxic substances on the body tissues is permitted.

We will now consider how the changes so produced affect particular tissues and the symptoms to which they give rise.

The Nervous System.—Reference has been made to the changes observed by Edmunds in the central nervous system in thyro-parathyroidectomized dogs. These need not be recapitulated except in so far as to say that they consisted in chromatolysis of cells of all parts of the central nervous system. Similar changes may be assumed to occur in myxœdema—at least in cases in which the thyroid apparatus is wholly destroyed. That this is to some extent the case has been shown by Mott in certain cases of sub-thyroidic insanity occurring in women about the time of the climacteric and associated with mental confusion, hallucinations, delusions of persecution, loss of memory for recent events and terminating in dementia. Mott has found in several such cases examined by him that the mental disturbances are associated with (1) "an atrophy of the glandular structure of the thyroid, interstitial fibrous hyperplasia and abundant infiltration of the same with lymphocytes; a condition of chronic inflammation arising from a toxic condition probably local in its source, as the parathyroids

show no change. (2) An increase of weight of the pituitary gland, and unusually abundant colloid in the *pars intermedia* which may be regarded as evidence of thyroid insufficiency." In these cases Mott found that " there is a universal chromatolytic change in the cells of the central nervous system sparing no system or group of neurones entirely." These changes were especially noted in the smaller cells of the autonomic nuclei, *e.g.* the vagus and glosso-pharyngeal. He did not find the characteristic chromatolysis in two other cases of simple atrophy of the thyroid without lymphocytic infiltration and without changes in the pituitary body, one of whom had been the subject of dementia with epilepsy, the other of confusional insanity.

Mott considers that these changes in the central nervous system may be due to " a toxic condition of the blood altering the osmotic membrane of the nerve cells and thus aiding in the imbibition of water," or " to absence of iodine-containing secretion, or of some substance normally provided by this secretion, which is essential for nerve cell-metabolism, and probably to both factors." The more important factor, however, is the thyroid secretion, since the mental condition improves under thyroid feeding.

In addition to the above changes, which occur in certain cases only, the nerve trunks are infiltrated and subjected to compression by the swelling of surrounding parts so that the transmission of all motor and sensory impulses is delayed (Hertoghe). There is also a distinct loss of excitability of the whole sympathetic nervous system, as has been shown by the experimental stimulation of the sympathetic nerves of thyroidless animals (v. Lyon, Falta). The diminution in sensitiveness of this system is also shown by the fact that the injection of adrenalin into thyroidless animals or myxœdematous subjects fails to produce glycosuria.

Mott has found chromatolytic changes in the sympathetic system in one case of sub-thyroidic insanity. No doubt changes similar to those occurring in the central nervous system are to be found also in the sympathetic system with some degree of constancy.

A similar depression of sensitiveness and conductivity occurs in the vagal nerves due to identical causes.

Symptoms referable to the nervous system are often amongst the earliest evidences of thyroidal defect; they may indeed be the predominant feature of myxœdema. These exhibit themselves as an increasing dullness of all mental processes: the patient begins to lack ideas, to lose his memory for recent events, to suffer from mental confusion, to become dull-witted, to find a difficulty in expressing himself: he may know what he wants to say but can't say it. His speech is sluggish as well as his mind; he has difficulty in articulation; he can't be bothered to talk, can't be bothered to make any mental effort; he becomes indolent and apathetic. He is always sleepy and drops off to sleep as soon as he sits down. But his sleep does not refresh him, and patients may complain of sleeplessness; in the sense that he gains no refreshment for body or mind, he is sleepless. He wakes up tired in the morning—more tired in fact than when he went to bed, and this matutinal fatigue is a very early and characteristic symptom, as well as a very common one; even in the milder cases it is frequently present. He suffers from headache which may be either frontal or occipital, usually the latter. It is worse in the morning and may pass off during the day. Patients may be so accustomed to it as to forget to mention it unless questioned (Hertoghe). He may suffer from vertigo and loss of equilibrium and is apt to stumble and fall on slight provocation. He is hard of hearing and may complain of noises in the ears. He may have visual and auditory hallucinations, hear voices, the ringing of bells, see flashes of light or animal figures before his eyes (Murray). It hurts and fatigues him to use his eyes. His sense of taste and smell may be disturbed, though this is difficult to determine. His sense of touch is lessened where thickening of the skin has occurred.

The loss of memory and mental confusion leads to depression or it may be to actual melancholia and dementia. Indeed, as Hertoghe has said, "melancholy is the predominating note of the myxœdematous subject, on the psychic side."

Nervousness and tremor may be early symptoms of myxœdema

(Horsley). Tetany is a common accompaniment, certainly in the Himalayas. The nervous symptoms described under "nervous cretinism" indicate the extent to which such symptoms may be the result of degenerative or developmental changes in the central nervous system in consequence of thyro-parathyroid defect. Symptoms referable to the cerebellum (gait, speech, etc.) have been reported in a few cases by Odin, which cleared up under thyroid medication.

The extent to which idiopathic epilepsy may be due to thyro-parathyroid defect is a question which should always be considered in such cases. These cases of epilepsy are, according to Bolton, often associated with chronic intestinal toxæmia, and he speaks enthusiastically of the beneficial effect of thyro-parathyroid therapy.

A perusal of the work of Mott and Kojima indicates the comparative frequency with which the victims of insanity are subthyroidic and the beneficial results to the patient which the recognition of this fact brings with it. In 100 selected cases of insanity examined by Kojima the thyroid gland was generally smaller than normal; in 12 per cent. of male cases and in 18 per cent. of female cases it was much smaller, and these were the subjects of hypothyroidism.

The lack of nutrition, infiltration and compression of the nerves give rise to neuralgic and lightning or rheumatic-like pains in various parts of the body and to difficulty and sluggishness of movement. The reflexes are weak; the knee-jerk may sometimes be absent. The gait is stumbling, slow and like that of a man exhausted after great physical effort. The movements of the hands are clumsy and slow and finer movements are executed with difficulty or not at all. The changes in the muscles (*vide infra*) are also in part responsible for these results.

Similar changes involving the sympathetic system give rise to various cardio-vascular and vaso-motor disturbances: the heart's action is impaired, the circulation is sluggish; the pulse is small and slow and may average only 40–60 beats per minute. The patient suffers from cold hands and feet, and from chilblains; he feels the cold intensely, and actual Raynaud's disease may be

present. The body temperature remains persistently subnormal. The sweat glands are inactive, even in hot weather or on exertion; pilocarpine does not induce sweating. The skin is dry and its electrical sensibility is diminished; the sebaceous glands are inactive, and the hair is dry and ill-nourished.

The involvement of the vagal nerves results in atony of the intestines and in constipation, which is further accentuated by the infiltration of the intestinal walls (*vide infra*). Dyspnœa and cyanosis are in part due to the same cause.

Finally, all organs actuated by sympathetic nerves are

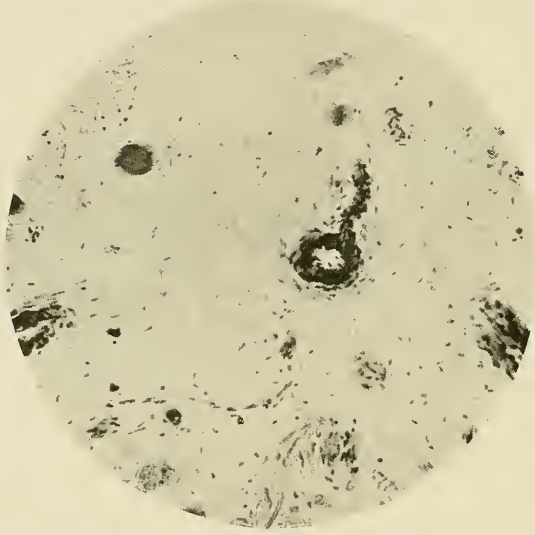


Fig. 72.—Section of myxœdematous skin. From a specimen in the possession of the late Sir Victor Horsley, F.R.S.

depressed in their function; the hormonic resources of the body are greatly impaired and metabolism is correspondingly disordered.

The Skin.—The characteristic infiltration of the skin and subcutaneous tissues in myxœdema, which has given to it its name, was originally thought by Horsley to be due to mucin; it is now known to be due to the deposition of a substance resembling mucus. Fig. 72, from one of Horsley's original preparations, shows the distension of the tissues with this

mucus-like substance; the specimen shows also vacuolated nuclei in fat cells. The myxœdematous process results in the proliferation of nuclei and in the formation of new connective tissue fibrils especially around the sebaceous and sweat glands and around the hair follicles (British Myxœdema Commission).

The skin of the entire body may be affected by this infiltration or certain areas are more distinctly involved than others, thus the tissues of the face and neck, the wrists and back of the hands, the ankles and feet, and the supra-clavicular fossæ are special seats for the deposition of myxœdematous material. The appearance of the hands is especially characteristic : their skin is dry and scaly, the nails are striated or cracked, the fingers are thick, and the whole hand has a " spade-like " appearance (Gull). The movements of the hands are clumsy; the finer movements are difficult or impossible—as in the case of a violin-player who found it increasingly difficult and finally impossible to use his instrument.

The face is putty-like or amber-coloured, and there is usually present a malar flush due to the presence of small venules. The eyelids are swollen, the palpebral fissures small; the eyes lack lustre and are opened lazily and with difficulty. The lips and alæ of the nose are thickened and swollen, as are also the ears. The whole face is mask-like and expressionless (figs. 73, 74). The skin feels elastic, does not pit on pressure, and is clay-like in texture (Halliburton). The epithelium scales off. Patches of pigmentation occur, especially on the face, forehead and neck. Various skin affections may occur : eczema, psoriasis, " milk-crust " in children (Hertoghe), leucodermia, sclerodermia, ichthyosis, warts in young people, acne vulgaris in childhood or adolescence (Morris), itching and burning sensations of the skin.

The hair falls out or becomes prematurely grey. It is coarse and dry, the sebaceous glands failing to oil it properly. A thick dirty crust is apt to collect on the scalp and around the roots of the hair. The hair first disappears from above the forehead —the " frontal band alopecia " of Walsh (fig. 74). Later it falls off from the nape of the neck—the " cassowary neck." The eyebrows fall out, especially the outer one-third; and this " eyebrow

sign," to which attention was first directed by Hertoghe, is one of great value especially as an aid to the detection of mild cases of the disease. The eyelashes also may disappear, and marginal blepharitis may occur. The axillary and pubic hair falls off in like manner.

The mucous membranes share in this process of infiltration. The conjunctivæ are thickened and are very apt to suffer from inflammatory states; lachrymation is frequent. The mucous membrane of the nose is similarly affected; that of the mouth,

FIG. 73.—Young man before the onset of myxœdema.

FIG. 74.—The same after the development of myxœdema.

(From photographs in the possession of the late Sir Victor Horsley, F.R.S.)

palate and uvula is pale in colour and much swollen. The gums also are swollen and pyorrhœa alveolaris is very common; the teeth may be covered with a greenish tartar at their roots. The breath is fœtid. The mucosa of the larynx and vocal cords is also involved, making talking difficult, the voice harsh and singing impossible. The loss of the high notes in the singer's voice is an early sign to which attention has been directed by Granger. An irritating cough is a common symptom. The tongue is thick and swollen, its whole substance being involved in the infiltration process, and may protrude from the mouth in young people.

It bears on its surface the indentations of the teeth. The tonsils are enlarged; the subjects of the disease are mouth-breathers and snore loudly. Adenoids are commonly present. The infiltration extends to the Eustachian tubes and the tympanic cavity, so that to the nervous defect this further element is added to impair the hearing.

The mucous membranes of the gastro-intestinal tract, of the bronchii, of the uterus, the vagina, and of the bladder are likewise involved in the process of infiltration.

The Bones, Cartilages, Ligaments, and Muscles.—The failure of nutrition leads to a cessation or retardation of the process of ossification in those cases where growth is not complete (infantile and juvenile myxœdema). Histological examination of the bones in young myxœdematous subjects shows a marked diminution in the size of the zone of cartilage proliferation, narrowing of the marrow-cavity, abundant fat-content in the marrow and poverty in cells of the marrow spaces (Falta). Hertoghe has called attention to a valuable prognostic sign which X-ray examination affords in these cases. Where the epiphysial junction is not obliterated growth is still possible, whereas when it is no increase in growth can be hoped for. The lack of nutrition of the bones is exhibited by the fact that in sub-thyroidic subjects fractures heal badly; Hertoghe believes that in all cases where thyroid medication has been successfully employed to aid the union of fractures the patients have been sub-thyroidic.

The disturbances in dentition in young subjects which accompany the cessation of the process of ossification have been referred to under cretinism. In older subjects the crowns of the teeth may become ground down leaving broad flat surfaces. In some cases observed in the Himalayas this was a very noticeable feature. The cartilages also are infiltrated and the joints are painful, stiff and may crackle. "If the hand is applied to the joint (knee) when flexed, there will be a sensation like the crackling of frosted snow. This is a very characteristic sign; indeed it is almost pathognomonic" (Hertoghe). "Rheumatic"

pains and soreness in the bones and joints are a frequent source of complaint, and true rheumatoid arthritis is not uncommonly associated with the disease. Hydrarthrosis may occur (Dalché).

The ligaments also are infiltrated and relaxed, and such conditions as pain in the sole, flat-foot, knock-knee and scoliosis may arise in consequence in young subjects. (Figs. 34, 60, 66). On the other hand, contraction of the palmar fascia and of the tendons of the hands may be evidences of hypothyroidism and be relieved by thyroid therapy (Levi; Pizarro).

The muscles are notably affected by this infiltration process. The muscle fibres are distended with fat and mucus-like material, their connective tissue as well as their aponeuroses and tendons being similarly affected (Stevenson and Halliburton). Consequently their contractions are sluggish and waste products accumulate in them owing to the impairment of circulation and drainage. All muscular movements are slow and executed with difficulty owing to their impaired enervation, as well as to their infiltration. The muscles of the abdominal wall are weakened and the abdomen protrudes; ptosis of the viscera and constipation is thus favoured. The muscles of the back of the neck are weak and permit the head to fall forward on the chest, a sign of importance in sub-thyroidic children.

The involuntary muscles are equally affected with the voluntary. Thus the heart's action is further impaired owing to the infiltrated state of its musculature, as is the action of the intestine from a like cause.

In consequence of the infiltration pains are complained of in various parts of the body, especially in the back and between the shoulders. Women may complain of pain in the arms and shoulders when doing the hair (Hertoghe). Pains in the feet and legs and cramps of the muscles are common sources of complaint, and a "giving way of the legs," especially when going uphill or upstairs, is a not infrequent symptom.

Cardio-vascular System.—We have seen that the heart shares in the process of infiltration; fat also is deposited between its fibres. This, together with the lack of sensitiveness and

infiltration of its nerves, combine to produce the sluggish circulation and the feeling of cold which is so characteristic. The pulse is slow and small, regular and of low tension.

These changes also account for the attacks of cardiac pain from which myxœdematous persons suffer. The endothelium of the vessels is impaired in its vitality; its permeability is increased and calcareous deposits occur in the vessel walls. Arterio-sclerosis is a common feature of the condition, and atheroma of the aortic arch is frequent, a fact which was first demonstrated by v. Eiselsberg in thyroidectomized sheep.

Hertoghe has drawn attention to the fact that symptoms of palpitation, precordial pain, or tachycardia may occur in sub-thyroidic subjects on the administration of thyroid extract owing to the rapid withdrawal from the heart-walls of infiltrating substances, to the loss of which the heart takes time to adjust itself. Such patients when kept in bed soon become accustomed to the drug and can tolerate it in moderate doses.

The Blood.—Anæmia is the rule. The reduction in the red blood corpuscles may amount to 2,000,000 or even to 3,000,000 and there is a corresponding loss of hæmoglobin. The reduction of hæmoglobin may amount to 50 or 60 per cent. Normal red blood counts are very rare. Nucleated red blood corpuscles may be found. Leucopænia is the rule; the total leucocytes may be reduced from 6,000 to 3,000 per c.mm. (Kocher). There is a well-marked lymphocytosis amounting to 30–40 per cent., while the polymorphonuclear leucocytes are diminished in numbers. Mast cells may be present (0·2–0·4 per cent.) and the eosinophil cells may be increased (Falta). The coagulation time of the blood is stated by Kocher and Kottmann to be decreased, but by Bauer to be increased, which is most in conformity with the clinical features, *e.g.* the tendency to hæmorrhages—epistaxis and menorrhagia. The blood-serum is more toxic than that of normal persons, and its bactericidal power is diminished (Fassin). There is an increased venosity of the blood (Horsley) and a diminution in the oxyhæmoglobin (Massin).

Respiratory System.—Here the lack of nutrition and infiltration of the vagal nerves, the infiltration and consequent weakening of the respiratory muscles and diaphragm, the infiltration of the lungs themselves, and the swelling of the mucosa of their bronchi and bronchioles all combine to produce a depression of respiratory function and a sense of oppression. Dyspnœa occurs on slight exertion or fatigue and may be so extreme as to cause cyanosis. These attacks of dyspnœa may resemble asthma and be mistaken for it (Hertoghe).

Sub-thyroidic subjects are very prone to attacks of pulmonary infection to which they readily succumb.

The Sex Organs.—As we have seen total loss of thyroid secretion causes failure of development of the sex organs and a condition of infantilism. In sub-thyroidic girls the ovaries and uterus either remain infantile when menstruation is not established or these organs develop late, resulting in amenorrhæa. When the thyroid defect arises later in life menorrhagia is the rule. The menstrual period is prolonged and the intervening periods shortened. Hertoghe considers that the infiltration of uterine mucosa and musculature as well as the diminished coagulability of the blood is responsible for the profuse menstrual discharge which is so characteristic of the condition.

Pregnancy and lactation usually improve the sub-thyroidic woman's state of health, but miscarriage is frequent. According to Landau, sterility may be one of the consequences of myxœdema owing to atrophy of the sexual apparatus, and the climacteric may occur prematurely. In rare cases of slight thyroidal inadequacy, improvement may occur after the menopause (Hertoghe), but as a rule it becomes worse at this period and after it.

In males sexual desire may be lost, and according to Hertoghe spermatorrhœa may occur. The labia in the female may be swollen.

The Kidneys and Bladder.—The infiltration and the impairment of nutrition of the kidneys proportionately impair their

function. The excretion of urine is diminished; as is the total nitrogen excreted. Its specific gravity is low, and albumin may be present (in 20 per cent. of cases only) or tube casts. Chronic Bright's disease is a common complication, and more rarely true diabetes may be a concomitant.

Infiltration of the neck of the bladder occurs early; its mucosa and muscular walls suffer later. Its epithelium is shed in large quantity and is readily detected in the urine; concretions are liable to form. Its susceptibility to infection is greatly increased. Consequently the desire to pass water is frequent, and urinary precipitancy and enuresis in young sub-thyroidic subjects are common symptoms. Parents and children might be spared much suffering by the recognition of the fact, to which Dr. Leonard Williams [1] has so frequently drawn attention of late years, that thyroid insufficiency is a frequent cause of enuresis. I have known children who have been so chastised for wetting the bed that their lives have been made a burden to them, and I have known of physicians who have countenanced and even recommended such chastisement. Had they prescribed small doses of thyroid extract instead of the cane they would probably have cured the child of its affliction and satisfied themselves that this "vice" has usually a pathological basis.

The Gastro-Intestinal Tract.—Here also the impairment of nutrition, the sluggish circulation, the enfeebled enervation, the diminution of the intestinal and gastric secretions, the infiltration of the mucosa and of the muscular walls, the swelling of the lymphoid follicles, all combine to produce a state of enfeebled digestion, impaired peristalsis, and imperfect drainage of the bowel. The weakness of the abdominal walls aids in the process; ptosis of the abdominal contents, obstinate constipation, intestinal stasis, increased fermentation and intestinal toxæmia are the outcome of these changes. Under these circumstances are developed those bands and "kinks" with which Sir Arbuthnot Lane's name is associated. Thus

[1] Leonard Williams: *Lancet*, May 1st, 1909; *British Jour. Child. Diseases*, June, 1909; *Med. Press and Circular*, May 5th, 1909.

intestinal stasis may be due primarily to sub-thyroidism and this is especially the case where the thyroid defect is congenital or acquired in early life (see page 138). If due to other causes the stasis once established may lead to sub-thyroidism by the action on the gland of the toxic products of bacterial growth in the static bowel, or the abnormal processes of digestion may interfere with the efficient elaboration of the thyroid's secretion thus reducing its physiological activity. A vicious circle is thereby established which in either event augments the thyroid defect as well as the stasis.

Anorexia is frequent and there may be a loathing of food, especially of meat. Thirst is rarely felt and the consumption of fluid is reduced to a minimum. It is extraordinary how little some sub-thyroidic women drink—a circumstance which in itself favours the obstinacy of the constipation. The function of the stomach is depressed and indigestion is frequent. There is a marked tendency to appendicitis (Hertoghe), and the "controlling appendix" of Lane is frequently met with in sub-thyroidic women. Attacks of diarrhœa may occur in myxœdematous subjects and are due to inflammatory states to which the intestinal mucosa as well as all mucous membranes are peculiarly prone.

Hæmorrhoids are common, and rectal hæmorrhage is frequent (Hertoghe). Myxœdematous swelling of the anus may occur.

The liver is enlarged, congested and infiltrated, and its function correspondingly impaired. The synthesis of urea is incomplete and there is an excess of ammonium salts in the blood and urine. The bile ducts are swollen and may become choked, and according to Hertoghe biliary calculi are of frequent occurrence. "Bile passes into the blood, giving rise to the icterus of myxœdematous subjects (amber coloration of the skin)" (Hertoghe). The production of anti-toxic substances by the liver—compliment, alexines—in which it is so intimately associated with the thyroid (Müller), is greatly interfered with.

Finally, the protective resources of the body are much impaired, with the result that its susceptibility to all kinds of infection is increased. Especially is such a condition likely to

result in the body's invasion by micro-organisms from the intestine or throat which in health may exist there harmlessly as, for example, the pneumococcus.

MINOR THYROID INSUFFICIENCY

I have endeavoured to make the foregoing account of the symptoms which may arise in consequence of the thyroid's atrophy as complete as possible, and to provide a morbid anatomical explanation of their origin, chiefly because a minute knowledge of these symptoms and their mode of origin is essential to the recognition of the many evidences of minor degrees of thyroid defect. It is rare that the thyroid is wholly atrophic and that we meet with the complete picture of myxœdema, but as has already been indicated, the minor manifestations of thyroid defect are of very common occurrence. One has but to observe the passers-by in the streets to notice the great frequency of Hertoghe's "eyebrow-sign," for example. Although this sign may not be pathognomic of sub-thyroidic states, it indicates the necessity for a search for other evidences of thyroidal incapacity, and insomuch as it is a sign which cannot be missed, its presence should immediately recall the condition—hypothyroidism—to the mind.

Emphasis has already been laid on the great importance of the recognition of the minor signs of thyroidal inadequacy in early life. Their recognition in later life is hardly less important. The profession is greatly indebted to such acute observers as Hertoghe, Leopold Levi, de Rothschild, and Leonard Williams for directing its attention to these minor manifestations of thyroidal incompetency. It will be well, therefore, to pick them out from amongst the mass of symptoms with which we have just dealt. As enumerated by these observers, they are: Transitory infiltrations, a not uncommon site is the back of the hand or areas of the body which are subjected to unusual fatigue; the "eyebrow sign," premature baldness, premature greyness; partial congenital alopecia; coldness of the hands and feet; chilliness; shivering fits; persistent subnormal temperature;

hypersensitiveness to cold so that neuralgic pains, lumbago and torticollis are readily induced; chilblains; blueness of the face, hands and feet; constipation; dysmenorrhœa and menorrhagia; undue mental and physical fatigue, especially matutinal; anorexia; somnolence; sleeplessness in some cases; obesity; trophic alterations in the skin; leucodermia; muscular and articular pain; frontal and occipital headaches, the latter matutinal; apathy, indolence, and, indeed, any of the symptoms in minor degree which have been mentioned under myxœdema.

These symptoms may be periodic, paroxysmal or transitory in their appearance, dependent on the intermittent action of those factors which depress the thyroid's function.

While no single symptom is in itself sufficient to justify the diagnosis of minor thyroid insufficiency, the occurrence of several will make such a diagnosis very probable, and justify the application of the therapeutic test of thyroid therapy.

Leonard Williams draws attention to the difficulty which is often experienced by the physician in eliciting from the patient precise information as to the existence of these symptoms. He writes:

"Sub-thyroidic people, like the fully myxœdematous, though voluble about irrelevant matters, often seem curiously reticent about themselves. Their brains move slowly and they are forgetful. It is therefore necessary to interrogate them very closely on questions which are purely subjective. That they are unduly sensitive to cold, that they have considerable difficulty in concentrating the attention, that their memories are unreliable, especially in small matters, that they are very somnolent, especially at certain times of the day, are all facts which must be elicited by cross-examination. Fatigue, muscular and mental, is very characteristic of the condition. Although this element is very rarely absent from a case, the fact of its presence is never volunteered. This is due as a rule to its having been quite confidently and often brutally attributed to 'nerves,' 'fancies,' 'vapours,' or whatever the epithet of the moment may happen to have been, and the patient has been urged to rouse himself and take plenty of exercise. Needless to say, this is very bad

advice, which not only causes a great deal of unnecessary suffering, but militates very decidedly against any tendency to improvement. Such patients demand physical and mental repose, and it should on no account be denied them."

Just as in the case of complete myxœdema, so the manifold expressions of the thyroid's subnormal action are met with much more frequently in the cold climates of the west than in tropical and sub-tropical regions. This is no doubt due, in part at least, to the more frequent occurrence in colder climates of such maladies as measles, mumps, influenza, tonsillitis, acute articular rheumatism and other common infectious depressants of the thyroid's function.

Diagnosis.—The diagnosis of myxœdema rarely presents any difficulty. In rare cases, however, the question of its differentiation from chronic Bright's disease, gout, paralysis agitans, or Dercum's disease may arise. But the resemblance to these affections is always superficial, and close examination will resolve all doubts. The application of the physiological test of thyroid feeding may assist in doubtful cases.

Treatment of Myxœdema.—The first essential in the treatment of all degrees of sub-thyroidism is to remove such causes of thyroid depression as may exist at the time of observation. These causes will be sought for amongst the nutritional, psychic and infectious factors we have dealt with. Thus the regulation of the diet will become the physician's first concern, and while he advises the use of a nutritious dietary he will exclude or limit such articles as meat, excessive nitrogenous food, alcohol, and common salt. Hertoghe advises the limitation of sugar, and having regard to the mucus-like nature of myxœdematous tissue, such a restriction can only be beneficial. The physician will prescribe the free use of water, preferably given hot, one hour before food so that the excess excretion of waste materials consequent on the administration of the specific remedy—thyroid substance—will be facilitated. He will insist upon physical and mental quietude and secure for his patient the best possible hygienic conditions of life which her means afford. And he will remove as far as

possible all infectious or toxic sources of thyroid depression. Thus, pyorrhœa alveolaris, constipation and intestinal toxæmia, which are common accompaniments—the last almost an invariable one—will be combated by suitable remedies. Finally he will prescribe thyroid substance.

With regard to the use of this specific there are certain very important points with which it is necessary to be familiar :—

1. The preparation employed should be such that the physician is aware of its strength in terms of its iodine-content. A standardized preparation should therefore be used containing a known quantity of iodine. Of such there are many in the market which are very reliable. My own practice is to use the B.P. liquor, where this can be procured freshly prepared, but to the busy practitioner this form of the drug is not so readily available as those prepared by the leading pharmacists. In cases of minor thyroid insufficiency it is well to prescribe the remedy, as advised by Williams, in a form which is not recognizable by the general public. Such preparations are now procurable.

2. It is essential to realize that patients who require thyroid substance can tolerate it in considerably smaller doses than perfectly healthy subjects. It is therefore necessary to commence with a small dose and to increase it gradually. My own practice is to begin with half to one grain at bedtime in adult cases, but it may be given in quarter-grain doses three or four times a day. The initial dose should never exceed this amount. In children it should be not more than one-quarter grain at bedtime or one-eighth of a grain twice daily. The smallest dose which produces the desired effect is that which should be employed. It is rarely necessary to administer more than five grains daily. Relatively smaller doses should be given to the old than to the young. Children bear it well.

3. It is advisable to reduce the dose in hot weather and to discontinue its use from time to time. Such periods of intermission of the remedy may in women be made to include the menstrual period. There are, however, certain cases of toxæmic goitre in girls associated with dysmenorrhœa in which its use during these periods is beneficial.

4. I have referred to the symptoms of so-called "thyroidism" which may follow excessive dosage—tachycardia, palpitation, diarrhœa, vomiting and mental excitement. Such symptoms never arise when the drug is administered with care and its effects carefully watched. Some degree of tachycardia and even cardiac pain—as stated by Hertoghe—may arise in consequence of the rapid withdrawal of the infiltrating material from the myocardium. The drug should not be discontinued on this account if the physician is sure of his diagnosis; but should the pulse-rate keep persistently over 95 while the patient is at rest, the dose is too high. A daily record of the pulse should be kept in all cases until the dose suitable to the case under observation has been arrived at.

5. A rise of temperature accompanies the use of thyroid substance due to the increased metabolism which it induces. The temperature in all sub-thyroidic states is sub-normal, and the dose should be regulated so as to keep the body temperature about the normal line.

6. In children the body-weight is a safe index by which to gauge the dosage; once the initial loss of weight, owing to the disappearance of myxœdematous and excessive fatty tissue, is passed, the child should put on weight steadily. Loss of weight indicates excessive dosage.

7. One sign of commencing intolerance to which Leonard Williams draws attention is coryza. A sudden and profuse nasal catarrh may, he tells us, occur in persons taking thyroid substance. He refers also to painless enlargements of the glands at the angle of the jaw as further evidences of thyroid intolerance. I have not observed these myself; it is well to be aware of the possibility of their occurrence.

8. Thyroid substance has a pronounced diuretic action, and, promoting as it does the flow of succus entericus, it relieves constipation. In excessive doses it may cause diarrhœa. The appearance of sugar in the urine is another indication of excessive dosage. Albumin may occasionally appear in the urine, but in the absence of kidney disease it does not indicate the necessity for the discontinuance of the drug.

9. Certain drugs aid the action of thyroid substance. These are arsenious acid, calcium iodide, bicarbonate of soda and grey powder. They possess the property of influencing the thyroid gland in some way. Arsenic, as we have seen, controls its hyperplasia. Sajous regards mercury as a thyroid stimulant. No small part of the beneficial action of these remedies is anti-toxic. The bicarbonate of soda helps to neutralize the acids produced in the course of gastro-intestinal fermentation, while the antiseptic and purgative action of grey powder, by relieving intestinal toxæmia, largely explains its beneficial effect. It is hardly necessary to remind the reader that care should be exercised in the prescribing of such drugs as arsenious acid, calcium iodide and grey powder over prolonged periods.

10. While taking thyroid substance the patient should be kept under observation and not permitted to use the drug indiscriminately.

When sub-thyroidic patients are first put on thyroid substance they may complain that the hair falls out in handfuls. It does so to make room for a luxuriant crop. This should be explained to them, otherwise they may refuse the remedy. Thyroid substance has only one effect on the hair of sub-thyroidic persons and that effect is good.

Quite recently Kendall has separated from the thyroid protein two iodine-containing compounds which appear to possess distinct therapeutic properties. The first—or α-iodine compound—exercises a profound influence on growth and, when administered in daily doses as small as $\frac{1}{180}$th of a grain, it produces in cretins a rapid increase in stature. Under its influence the mental activity of myxœdematous subjects is greatly increased, the skin condition is improved, somnolence disappears, the hæmaglobin-index rises and the sensation of cold is no longer felt. The daily dose should rarely exceed one m.gm. The β-compound, on the other hand, has no influence on growth but relieves the itching of the skin, the soreness of the bones and joints and the cramps in the muscles.[1]

[1] "Endocrinology," 1917, I. 2, pp. 153–169.

SECTION 11

GRAVES' DISEASE

Synonyms.—Basedow's Disease (1840); Parry's Disease (1825); Flajani's Disease (1800); Hyperthyroidism; Hyperthyrosis; Exophthalmic goitre.

Definition.—A disease characterized by heightened excitability of the whole sympathetic nervous system, greatly increased metabolism, abnormal action of the heart and of the thyroid gland, and disordered states of other hormone-producing organs. Its cardinal signs are tachycardia, exophthalmos, tremor and goitre; its terminations recovery, death or myxœdema. Its causal agent is unknown but is probably of infectious origin.

Prevalence and Distribution.—A great part of the mystery which surrounds this disease is due to the almost complete lack of epidemiological research with regard to it. In no country has its house-to-house distribution been studied and its prevalence and distribution scientifically determined. Thus we know nothing of its climatic, geographical or orographical distribution, of the influence of race, of season, of altitude, of its prevalence in town or country, or of its incidence amongst the rich and poor. Until we are in possession of authoritative information on these points we must continue to grope in the dark for its causal agent or at least to be hampered in our search for it.

Graves' disease is stated to be more common at the sea-coast than in inland tracts, but this is an impression only and is not based on extensive statistical research. It is, however, very rare in regions where goitre is endemic. Amongst the indigenous inhabitants of goitrous tracts of the Himalayas I have seen only comparatively few cases in ten years, though cases occur not

infrequently amongst European residents in such localities. It is said that this observation does not hold good of France and Switzerland or of the region of the great lakes of North America (Dock), but Bircher's experience in Aarau in Switzerland is similar to mine in the Himalayas.

Cases have been reported as occurring in dogs, cows, and horses, but these are as rare as their true nature is doubtful.

Heredity and Predisposition.—Heredity appears to play an ill-defined part in the genesis of this disease as it does in all abnormal states of the thyroid apparatus; certainly there is a decided family predisposition to it. It is not uncommon to find that two or more members of the same family are sufferers, while in such families diabetes, neuroses and even psychoses occur not infrequently (Falta). A congenital instability of the nervous system is a factor which may determine the onset of a considerable number of cases.

The children of women who suffer from Graves' disease are likely to be abnormal in some way.

Age and Sex.—While cases of Graves' disease have been noted to occur in infancy and childhood, it is rarely found before puberty. When it does occur before this period it may develop about the time of the second dentition. Of 3,477 cases collected by Sattler only 184 were in children under 15 years of age.

It is much more common in females than in males: thus Sattler found that of 3,800 cases 3,210 were in females, or 84 per cent.

Murray, in England, recorded 180 cases of whom 10 only were in males; while of 438 cases recorded by Mackenzie 393 were females and 45 males, or about 9 to 1.

The disease is almost entirely confined to the period of sexual activity in the female. Cases rarely develop in women after the age of 45, while in men they occur with comparative frequency after that age.

The series of 438 cases recently published by Dr. Hector

Mackenzie [1] provides some interesting features. Of these 263 were hospital patients, of whom 239 were females and 24 were males; 175 were private cases, of whom 154 were females and 21 males.

A percentage-distribution chart which I have prepared from Mackenzie's figures (fig. 75) shows graphically the contrast between the two classes, to which he has drawn attention.

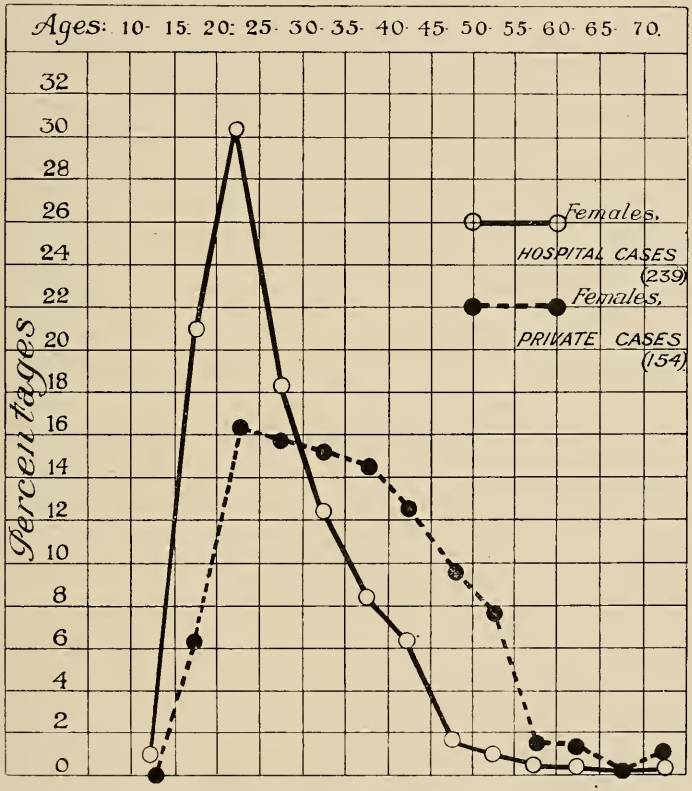


Fig. 75.—Chart showing percentage age-distribution at onset of Graves' disease in females of the richer and poorer classes. (Prepared from Dr. Hector Mackenzie's figures.)

This chart deals with females only and it may be taken as a fair example of the percentage age-distribution at the onset of the disease in women of the richer and poorer classes. It shows (1) that the onset is relatively later in the well-to-do than in the poor; (2) that the great majority of all cases in females of the

[1] Bradshaw Lecture, *Lancet*, Nov. 11, 1916.

poorer classes develop between the ages of 15 and 35 years ; (3) that in richer women the age of onset is prolonged over a further period of 10–15 years ; (4) that nearly twice as many cases arise in the earlier years of sexual life in the poorer as in the richer class females.

In contrast to this are Mackenzie's figures for males ; 9 per cent. of his cases in the poorer classes were in males, while 17·7 per cent., or about double the number, were males amongst the richer classes.

While these data are too limited to admit of any definite conclusions, they suggest that the factor of nutrition may play a more important part in the genesis of the disease in females of the poorer classes. In the rich another ætiological factor is probably more prominent—and one which affects males as well as females—it may be mental stress, social and business worry, or over-indulgence.

A chart such as this serves to indicate the important results which may be expected to accrue from epidemiological study of this disease.

Ætiology.—The ætiological factors which favour the onset of Graves' disease are those which we have seen determine all departures of the thyro-parathyroid glands from the normal state : these are nutritional, psychic, and infectious.

Briefly recapitulated these factors are (1) insufficient food or over-indulgence in food, and the disorders of nutrition to which these and chronic debilitating diseases give rise. Amongst the most important of such diseases are chronic constipation, intestinal disorders generally, and chiefly intestinal stasis. (2) Fright, mental distress and worry, business or social cares, unfortunate love affairs, violent emotion, and mental and physical exhaustion with loss of sleep such as occurs amongst soldiers in the trenches. (3) Attacks of acute infectious diseases, notably influenza, tonsillitis, rheumatic fever, typhoid fever, tuberculosis, secondary or hereditary syphilis ; naso-pharyngeal and uro-genital disorders, pyorrhœa alveolaris and helminthiasis.

As in myxœdema so in Graves' disease the onset of a proportion

of cases may be precipitated by some accidental circumstance, such as a train disaster, a fall from a horse, or by such circumstances as seduction, attempted rape, or the excitement and strain of war.

The ideal conditions for the development of the disease are provided when all three classes of factors—nutritional, psychic and infectious—operate on the individual at the same time or where two of them do so. They are predisposing causes only which favour the action of the underlying causal agency.

This agency is one which gives rise to continuous excitation of the sympathetic nervous system. That symptoms similar to those of exophthalmic goitre can be induced by the continuous excitation of this system is shown by the experiment of Cannon where the phrenic nerve was joined to the peripheral portion of the cut cervical sympathetic in the cat.[1] The operation resulted in tachycardia, increased excitability, loose motions, exophthalmos on the operated side, and in increase of the body metabolism as well as in an increase in size of the adrenals. In seeking for the source of the excitant of these symptoms in Graves' disease one is reminded that effects similar to those caused by stimulation of the sympathetic nervous system are produced by certain amines, resulting from the putrefactive decomposition of proteins or amino-acids in consequence of bacterial action.[2] The most common source of these amines is the gastro-intestinal tract.

The extraordinary influence of gastro-intestinal toxæmia in the genesis of Graves' disease is exemplified by a case recently admitted under the care of Sir Arbuthnot Lane at Guy's Hospital. The subject was a girl of 19½ years of age who developed, in South Africa, Graves' disease of very severe type. The condition was of some eighteen months' standing. She had a marked rheumatic history, having had chorea at the age of seven years, tonsillitis, rheumatic fever and chorea at nine years, and "nervous debility" for six months at thirteen years. She had suffered from palpitation from the age of eleven. On admission to

[1] Cannon, W. B., *Boston, Mas., Journal*, 1916, clxxv, 16, p. 564.
[2] Barger, G., *The Simpler Natural Bases*, London, 1914.

hospital she presented the following symptoms: great emaciation, dull abdominal pain, recurring attacks of nausea and vomiting, goitre of small size, prominent exophthalmos, tachycardia, severe palpitation and a heart's action so violent as to shake the bed, great pulsation of the carotids, abdominal and iliac arteries, great muscular weakness, pronounced tremor with a tendency to drop things, great nervousness, dizziness, severe headache, flushings, subjective sensations of heat, suppressed menses, loss of and greying of the hair, voracious appetite, and albumin and sugar in the urine—in short a case so typical and so severe as to leave no room for doubt as to its nature.

Röntgen-ray examination by Dr. Jordan revealed the presence of a greatly dilated stomach with pyloric spasm, an elongated duodenum and a state of chronic irritation of the colon resulting in unduly rapid emptying of its contents.

Sir Arbuthnot Lane performed gastro-jejunostomy and removed an anchored appendix which exerted a most marked control upon the ileal effluent, and freed a very tight terminal kink at the junction of the ileac and pelvic colon. The operation was performed on the 21st January, 1916, and was followed by two weeks' considerable pyrexia. At this time the patient's weight was only 4 st. 10 lbs., but following the return of the temperature to normal she began to put on weight and to improve in the most remarkable way. Seen on the 20th October, 1916, her weight had increased to 8 st. 5 lbs., the exophthalmos had totally disappeared, the palpitation was completely gone, and the tachycardia was greatly lessened, menstruation had returned, the muscular weakness, headache, vomiting and all other symptoms, with the exception of the small goitre, had disappeared. The goitre was but little altered in size and persisted doubtless owing to fibrotic changes. The patient felt and looked a different being and could walk for a considerable distance without fatigue, while the greyness of the hair had disappeared and its scantiness was replaced by a luxuriant growth.

Here then is a case of surpassing interest in which the symptoms of Graves' disease are definitely shown to have resulted

from alimentary toxæmia. This case was complicated by old rheumatic affection of the heart, but apart from this and the organic changes which had resulted in the thyroid all other symptoms disappeared as a result of the abdominal operation and of this alone.

It is interesting to recall in this connexion that in cases of Graves' disease with gastro-enteroptosis cure of the disease has been reported in several cases by the use of the Rose abdominal adhesive straps (Bate).[1]

Ebstein [2] reports four cases of true Graves' disease in which the symptoms disappeared as a result of treatment of intestinal stasis. In one case the patient, aged 42, showed decided improvement following the correction of the fæcal stagnation. The exophthalmos and the palpitation diminished, and the pulse-rate, previously 120, fell to 92–112. These were the more immediate effects, but soon all symptoms disappeared, the thyroid merely remaining slightly larger than normal. Some years later the patient was again seen and found to be in good health. Three cases have been reported by Hemmeter in which a chronic colitis preceded the Graves' disease by 10, 18 and 20 years, and in which the symptoms of the latter malady were greatly improved by attention to the colon.

These observations emphasize the great importance of the thorough X-ray examination of the alimentary canal by a competent observer when searching for an ætiological cause in individual cases. As we shall see dilatation of the stomach and gastro-intestinal disturbances are common precursors of this disease.

A further method of investigation to which it is necessary to refer is the routine examination of the fæces in all cases by every means at our disposal, and where possible their bacteriological examination for the detection of organisms to which the patient's resistance is low. It is well also to have the patient's Wassermann reaction determined in cases where there is the least shadow of

[1] Bate, A. R., *Monthly Encyclopædia and Medical Bulletin*, vol. xvii., No. 9, 1914.

[2] Ebstein, *Quinzaine therapeutique*, Nov. 10, 1913.

suspicion of syphilitic taint. A considerable number of cases are now on record where such examination has yielded valuable information; if necessary the parents of the sufferer should be examined by this means.

A careful examination of the mouth, naso-pharynx and nasal sinuses is also of great importance. Pyorrhœa alveolaris is very common in this disease, while the presence of such troubles as septic tonsillitis and rhinitis may be of considerable ætiological significance.

These are the main directions in which it is necessary to search for foci of infection; but there is no disease in which it is of greater importance to use every means which the science of medicine provides in the thorough and systematic examination of every case.

MORBID ANATOMY AND SYMPTOMATOLOGY

Few organs or tissues escape injury in this disease, consequently the symptoms which may develop in its course are most diverse.

A consideration of the anatomical findings, as they are at present known to us, will enable us to ascribe to them their meed of importance and to arrive at a clearer conception of the origin of the malady's manifold symptoms.

"It is on account of the attempts which have been made to raise the anatomical changes of certain tissues (formerly the nervous tissues, now the thyroid gland) to the *rôles* of primary factors that conflicting hypotheses and controversies have arisen" (Marine and Lenhart).

The Thyroid Gland.—While goitre usually results from the thyroid hyperplasia which is, as a rule, the accompaniment of all true cases of Graves' disease, enlargement of the gland is not invariable (fig. 76), nor does the severity of the symptoms bear any definite relationship to its size. Indeed, the symptoms are often severest where the thyroid is small and where it may not even be palpable, while milder cases may be associated with goitres of large size. The reason for this is now obvious. The size of the

gland is largely a question of individual nutrition, of individual powers of response to stimuli affecting the thyroid and of the virulence and constancy of action of the exciting agent. Thus there may be extensive alterations in the gland's structure without enlargement, and even with some degree of diminution in size. Cases in which goitre is absent are, however, rare; they amount to 4·3 per cent. in Murray's series (fig. 76).

Fig. 76.—Case of Graves' disease without goitre. (Dr. Mutch's case.)

The thyroid is usually palpable and enlarged to a greater or lesser extent. As a rule the swelling is slight or of moderate size; its surface smooth or granular, its consistency firm and elastic. It may be tender on pressure, and its size can usually be reduced by squeezing. Its vessels are greatly engorged and the whole organ visibly pulsates. This pulsation may be transmitted from the carotids, but as a rule, it arises from pulsation in the vessels of the gland itself. The pulsation is palpable,

and a thrill may be communicated to the examining hand. A bruit, systolic in time, is often heard over the organ. This bruit is a sign of considerable diagnostic import, as it is rarely found in simple goitre.

The thyroid swelling may commence as a "simple goitre," usually of the toxæmic variety—the symptoms of Graves'

Fig. 77.—Case of Graves' disease some years after operation for its cure. The scar of the operation is visible in the picture. (Reproduced by courtesy of Dr. Leonard Williams and the editor of *The Practitioner*.)

disease being super-added; but in endemic localities goitrous persons are no more prone to Graves' disease than are those who are not goitrous, indeed it would almost seem that they are less so. Again Graves' disease may be superimposed on a goitre due to fœtal or simple adenomata, or it may commence in a thyroiditis due to some acute infection, whilst in rare cases the thyroid gland may be normal or contain only small scattered

areas of hyperplasia (Marine, Lenhart, Halsted, MacCallum). Most commonly, however, it arises gradually in association with the other symptoms of the disease. It is usually an early symptom, but may appear later than the tachycardia or the exophthalmos. Occasionally, it arises suddenly and within a few hours. I have seen three such cases.

While it is necessary, therefore, to recognize that in Graves' disease the thyroid almost constantly undergoes pathological changes of great importance, we must recognise also that it does so in common with other organs and tissues of the body, and not seek to attribute to its changes a paramount importance which they do not justify.

Its histological changes have already been discussed (figs. 10, 21). The important factor in their genesis is the continued action of the excitant, which admits of no period of rest and of little recuperation so that cell-death and atrophy must sooner or later supervene. It will be recognized that these changes will vary in proportion as they have developed in a previously healthy gland, in a gland already affected by simple goitre or thyroiditis, or in a gland the seat of simple or fœtal adenomata; but in all cases the sequence of histological events is the same—hyperplasia, cell-exhaustion, atrophy and fibrosis. As a rule the gland is soon empty of colloid and of iodine, but where the disease has been engrafted on a colloid goitre colloid substance may be found in the organ owing to its retention in the vesicles by fibrous overgrowth and lymphatic stenosis. In such cases it is stated, but with insufficient reason, that the symptoms may be less marked and that they vary with the amount of colloid in the gland.

As a rule the hyperplastic process affects the whole gland equally, giving rise to a diffuse, vascular swelling of the organ; but occasionally one lobe may be more affected than the other or the areas of hyperplasia may be disseminated in small islets throughout an otherwise healthy-looking gland. It is stated by Barker that the hyperplastic process may not involve the gland itself, but may affect an accessory thyroid most often in the form of an intra-thoracic goitre. I should think such an event is excessively rare.

One striking feature in which the hyperplastic thyroid of Graves' disease differs from that of simple goitre is in the much greater degree of lymphocytic infiltration which occurs in it. Indeed, some authors consider that it is only where lymphoid proliferation is found, that the condition can be considered to be one of true Graves' disease (Roussy and Clunet). This feature of the thyroid is in conformity with the generalized lymphatic hyperplasia and with the lymphocytosis which is present in this malady.

As we have seen in a preceding section the changes in the thyroid are accompanied by qualitative as well as by quantitative alterations in its secretion. There appears to be little doubt but that these result in the secretion's physiological depression per unit of volume and in such disturbances of its biochemical balance as impart to it a toxic quality. For example, a substance is produced in the gland in Graves' disease which has a powerful action in reducing the blood-pressure.[1] To these alterations in the thyroid's secretion are due a number of the symptomatic features of the malady. These result in part from the secretion's influence on metabolism and on the adrenal-sympathetic system, and in part from the gradual impairment of the gland's function.

The Parathyroid Glands and Pituitary Body.—Changes have been described in these organs, but they are neither constant nor characteristic. They are in all probability induced to some extent by the same primal agency which induces the changes in the thyroid and other organs, and the fact that changes have been less frequently described in them does not necessarily mean that they are less common, but rather that they have been less thoroughly studied. Indeed, the same comment applies to the morbid anatomical changes described up to the present time in all other organs in this malady. The thyroid gland has for so many years played the star part in the drama of Graves' disease that too little attention has been paid to less prominent performers, and indeed its author's identity has for this reason been to a great extent obscured.

[1] *Jour. Phys. et de Path. gen.*, 1911, No. 6.

Within the last few years, however, other organs and tissues have received more attention, and our knowledge has correspondingly increased. Thus, for example, in the case of the lymphatic structures of the body important changes are found.

The Thymus and Lymphatic System.—The constancy of the persistence of the thymus and of its hyperplasia in this disease has been pointed out by many observers. It is, according to Simmonds, enlarged in 75 per cent. of cases. " The degree of hyperplasia varies with the age of the patient, with the duration and severity of the disease, with the state of nutrition and most certainly with other still unknown factors " (Marine and Lenhart). The spleen also is often enlarged while its lymphoid tissue shows a general increase. This tissue is also increased in the thyroid, the liver, the kidneys, the intestines and the bone marrow (Marine and Lenhart), while the bronchial, mesenteric, cervical, axillary and inguinal lymphatic glands may be enlarged. The deep cervical glands are always found enlarged at operation (Dock). Adenoids and enlargement of the tonsils are commonly present.

As the disease progresses and with increasing age the hyperplasia of the lymphoid tissue of the thymus gives place to atrophy of its cells and to sclerosis—a process similar to that which takes place in the thyroid gland (Marine and Lenhart).

The lymphocytic increase has been attributed to the association of Graves' disease with a status lymphaticus. This may be so in some cases, but there is good reason to believe that the lymphoid and thyroid hyperplasia have a common toxic origin.

In connection with the persistence or the disappearance of the thymus, it is interesting to recall the fact, referred to in an earlier part of this work, that the occurrence of a septicæmia, naturally acquired or artificially-produced, is capable of causing pronounced atrophy of the thymus in pigeons. Such a condition may in some cases be lethal for the gland, but it seems probable that a minimal action of certain bacteria or of their toxins may be capable of giving rise to its hyperplasia as in the case of the thyroid.

" The enlargement of the thymus is a contra-indication for

thyroidectomy, for after operation such cases frequently get worse, owing, it is believed, to thymogenic auto-intoxication" (Biedl).

The Blood.—The changes in the blood are represented by a diminution in the number of the polymorphonuclear leucocytes, and an increase of the lymphocytes, both large and small, often amounting to as much as 50 per cent. A mild leucopænia may be present but, as a rule, there is little alteration in the total number of leucocytes, their numerical changes being relative. Sometimes there is a marked increase in the eosinophile cells—a finding which should direct attention to the intestinal tract for the existence of worms. The coagulability of the blood is slowed (Lidsky, Bauer). The red blood-corpuscles and hæmoglobin-index are normal in those cases which are not associated with chlorosis or other forms of anæmia, which are common accompaniments.

These blood-changes are common to Graves' disease as well as to simple goitre and myxœdema and they occur, as is well known, in many other affections—notably intoxications and intestinal disorders. While they are in no way specific or characteristic, Marine and Lenhart have noted that there "is a close parallelism between the percentage of mononuclear cells in the circulating blood and the extent of the active lymphoid and thyroid hyperplasia. The blood-examination is, therefore, the most accurate clinical means of judging of the extent of active lymphoid hyperplasia and, while in no sense specific of exophthalmic goitre, is a fair index of the severity of the disease."

Lampa and Deutsch have obtained, by means of Abderhalden's reaction, results which appear to indicate the presence in the serum of sufferers from Graves' disease of special ferments which act on the ovaries, the thyroid and the thymus but on no other organs. The serum also causes dilatation of the pupil of the enucleated frog's eye (Kraus).

The bacterial alexines of the blood-serum are diminished (Fassin, Marbé).

A powerful depressor substance is present in the blood of

individuals suffering from Graves' disease (Sanford and Blackford) which is comparable in its action to peptone in 10 per cent. solution. It appears to me to be highly probable that this substance is derived from the gastro-intestinal tract.

Nervous System.—No constant or characteristic changes have been found in the nervous system in this disease, mainly because extensive pathological study of this system has not been so far undertaken. Small hæmorrhages and areas of softening are occasionally met with in the brain and medulla, or more rarely atrophy and sclerosis of one or other restiform body (Marine and Lenhart). Tedeschi has stated that he has produced symptoms simulating Graves' disease in animals as a result of experimental lesions of the restiform bodies, and that he failed to produce these symptoms in thyroidectomized animals. In the cervical sympathetic ganglia Wilson[1] has found various stages of degeneration—hyperpigmentation, chromatolysis, atrophy and fibrosis—in all of thirty-one cases examined. He considers that these changes are the result of active stimulation and over-function of the ganglionic cells, and that they run parallel to the stage and intensity of the hyperplasia in the thyroid and regress as the goitre regresses. In cases where symptoms simulating exophthalmic goitre had been produced in animals by the injection of Kendall's α-iodine these changes in the sympathetic ganglia were not found, nor did Wilson find them in persons who had died from causes other than Graves' disease. It appears probable that they are due to the same toxic irritant which produces the changes in the thyroid gland and other organs of the body. Lesions of the peripheral nervous system and the spinal cord have been described, but they are neither constant nor characteristic. "The absence, however, of any constant gross lesion does not preclude the possibility that the central nervous system is profoundly affected, but suggests," as Gowers states, "that the morbid state of the nervous system is one of that finer cell nutrition that still baffles our means of investigation" (Marine and Lenhart). It is probable that chromatolytic changes may

[1] Wilson, L. B., *Am. Jour. M. Scien.*, Phil., 1916, clii. 799–812.

occur in the nerve cells of the cerebral cortex similar to those found in shock resulting from trauma, emotion, various toxic conditions and anaphylaxis (Crile).

The heightened excitability of the sympathetic nervous system is the most important feature of this disease. Thus, the functional activity of all organs over which we have no voluntary control: the heart, the glands, the intestines, the respiratory apparatus, is subject to sustained or sudden increase. The following are the main symptoms to which this sympathetic hyper-sensitiveness gives rise:

1. *Exophthalmos:* This cardinal symptom of the disease is associated with widening of the palpebral fissure (*Dalrymple-Stellwag's sign*). It is due to the sustained contraction of the levator palpebralis muscle, causing contraction of the lids and exposure of the sclera, as well as to contraction of the protrusor bulbi muscle of Müller, which has a sympathetic innervation, causing protrusion of the globe. Exophthalmos is not an invariable symptom; it is said to be absent in about 25 per cent. of cases. It usually appears gradually and somewhat later than the other cardinal symptoms of the disease. In cases arising in consequence of trauma or fright it may appear in the course of a few hours. It is usually symmetrical, but may be unilateral and is then not infrequently associated with a unilateral enlargement of the thyroid on the same side. In Cannon's experiment on cats, to which reference has already been made, the exophthalmos on the operated side disappeared in one case on extirpation of the thyroid on that side. It varies greatly in degree from a heightened glitter and staring eye to the most intense bulging and even in rare cases to displacement of the globe. It also varies greatly at different times in the same individual. At one time, especially when the patient is quiet, it may be scarcely noticeable; at another, and under slight mental excitement, it is a prominent feature. This variation may be due in part to alterations in fulness of the vessels of the eye. Its severity bears no relationship to the severity of the other symptoms. An increase of the intra-orbital fat has been found at post-mortem; but this is a secondary deposit and not the cause of the protrusion.

It has long been known that experimental stimulation of the cervical sympathetic will produce exophthalmos, an observation which we owe to Claude Bernard; Cannon's experiment on cats provides additional proof of the fact. The relationship of exophthalmos to the degree of thyroid hyperplasia has been worked out by Marine and Lenhart, who have arrived at the following conclusions: "The fact that exophthalmos may be present either with the thyroid normal or with any degree of thyroid hyperplasia, and that there may be a marked thyroid hyperplasia without exophthalmos points strongly against the view that thyroid hyperplasia is ætiologically related to exophthalmos and towards the view that both phenomena are parallel, though often not synchronous, manifestations of a fundamental and more obscure nutritional disturbance."

Exophthalmos cannot be produced experimentally in animals by thyroid feeding. Positive results have been recorded in a few instances in Germany following on the administration of doses out of all proportion to the weight of the animal, and even then these results, as recorded by Falta, amounted only to "a not very marked degree of exophthalmos." Such findings cannot be admitted to outweigh those of the many experimenters who have consistently failed to produce the condition by thyroid feeding. It is interesting to recall in this connexion the observation of Gley[1], in 1910, that exophthalmos developed slowly in a rabbit from which he had removed the whole thyroid apparatus. Exophthalmos is not due to excessive action of the thyroid, but to excessive action of the adrenals, as has been shown by Maurice of Lyons.[2]

The rareness of involuntary winking, which is associated with the exophthalmos, is known as *Stellwag's sign:* the failure of the upper lid to follow the eyeball in its downward movements, as *v. Graefe's sign:* the weakness of convergence of the two eyes, as *Moebius's sign.*

Vision is, as a rule, not deranged by these changes. Corneal

[1] Gley: "Comptes réndus des sciences de la Société de Biologie," 1910, t. lxviii. p. 858.

[2] *Lyons Medical*, Oct. 20, 1912.

ulcer due to constant exposure and inflammation of the whole eye, may, however, occur. Ophthalmoscopic examination of the eye-grounds reveals dilation of the retinal vessels, while optic atrophy has occasionally been noted as a late sequel. Weakness and paralyses of various ocular muscles may occasionally be found, the eye muscles sharing in the general muscular weakness which is such a striking feature of the malady.

The instillation of adrenalin into the eye sometimes produces mydriasis (*Loewi's sign*). The size of the pupils varies ; dilatation occurs only rarely. Curschmann calls attention to the dissociated reaction of the pupils—the reverse of the Argyll-Robertson sign—which he finds in exophthalmic goitre and has never encountered except in this disease.

The eyelids may be swollen and œdematous, more usually they are pigmented. There may be an excessive secretion of tears or an abnormal dryness of the eye, and the conjunctiva may be unusually bright and glistening. Tremor of the lids when closed and even of the bulb may occur. Occasionally a bruit may be heard over the eyeball but is in no way pathognomonic.

2. *Tachycardia :* this is one of the earliest as well as the most important of the four cardinal symptoms of the disease. It is due to the continued irritation of the sympathetic nerves to the heart. But the tachycardia may also in part be due to the sustained dilatation of the peripheral arterioles and to the increased metabolism. Gley considers that it is due to the action of certain toxic substances which he believes are produced in the thyroid gland as a result of its abnormal activity ; it is probable that his observations may be capable of explanation on the ground that these substances are largely of intestinal origin.

Reports as to the effect of experimental thyroid feeding on cardiac action vary greatly, but it appears to be true that in animals even when this is administered in toxic quantities the pulse is not affected (Carlson, Rooks and McKee) while in man it is more likely to be so. It has always seemed to me that thyroid feeding in excess is much more likely to accelerate the pulse in cases where the thyroid gland is incompetent than in perfectly healthy subjects ; it is certainly then that care needs to be

exercised in its use. Many healthy persons can take thyroid substance in considerable doses for prolonged periods without the slightest ill effect, but there are others in whom the pulse-rate is quickly accelerated. We must, therefore, recognise the possibility of individual idiosyncrasy in this as in other medicaments.

The relationship of the pulse-rate to the degree of thyroid hyperplasia—that is to say, to the volume of secretion poured into the blood—is very important in view of the prevailing opinion as to the thyrogenic origin of this symptom. Marine and Lenhart as a result of extensive histological observations have concluded "that the differences between the pulse-rates of the normal or colloid glands and of the most marked active hyperplasia are so slight as to bear no suggestion of any causal or effect relation. If any relation exists the objective evidence would tend to indicate a hyposecretion rather than a hypersecretion, since the pulse-rate bears no relation to the amount of secreting surface, and a negligible relation to the histological structure of the gland. Also the histological structure and the iodine-content may be reversed in a given case without necessarily producing any modification of the cardiac activity; and adenomata may be associated with the same pulse-reaction as ordinary hyperplasia.

It does not appear from the evidence at present available that the explanation of the cardiac activity is so superficial or simple as either a thyroid hypersecretion or hyposecretion would indicate, but both the cardiac activity and the thyroid reaction are parallel manifestations consequent on some more general and remote disturbances."

Not only does the thyroid hyperplasia bear no direct relationship to the pulse-rate, but the excess of α-iodine (thyroid hormone) in the blood-stream, which results from it, appears to be only indirectly responsible for the tachycardia. Experiment has shown that after the administration of this substance there is no apparent effect for many hours. "There is no increased pulse-rate or drop in the blood-pressure. If, however, amino-acids are injected simultaneously the pulse-rate is enormously increased" (Kendall).[1] These findings appear to me to provide a further clue

[1] Kendall, E. C., *Boston M. and S. Journal*, 1916, clxxv., No. 16, p. 557.

to the nature of the substances responsible for the heightened cardiac action in Graves' disease. They are, I believe, the poisonous decomposition products of amino-acids—monamines and diamines—which may be formed in the organism wherever proteins or amino-acids are exposed to the action of bacteria—and especially to the action of anaërobic bacteria in the gastro-intestinal tract.[1] These highly virulent poisons may not only initiate the histological changes in the thyroid gland but, by their direct action on the adrenal-sympathetic system or by their chemical interaction with the gland's secretion and the disturbance of its normal balance, they may give rise at the same time to the tachycardia.

The pulse is usually rapid and forcible; its rate may vary from 80–160 beats per minute, more rarely it may run as high as 200. It varies greatly in the same individual at different times. A pulse persistently over 95 while the patient is under observation in bed is suggestive of this malady.[2] The cardiac disturbance is exaggerated more readily by emotional factors than by physical exertion. The palpitation may be very distressing to the patient; and in some cases the heart's action is so forcible as to cause the chest to heave, or even to shake the bed. Arrhythmia is not uncommon. There is usually present some degree of hypertrophy and dilatation with relative incompetency of the valves. The cardiac dulness is sometimes increased; the apex-beat may be displaced and a systolic thrill may be felt. Various murmurs may be heard. These are in proportion to the degree of myocardial insufficiency or to the extent of pre-existing organic changes of rheumatic origin. Albuminuria may be present; albumosuria is the rule.

Fatty degeneration and brown pigmentation of the muscle-fibres, with varying degrees of arterio-sclerosis of the cardiac

[1] Barger, G., "The Simpler Natural Bases," London, 1914.

[2] The injection of 1 c.c. of an extract of the posterior lobe of the pituitary body—equivalent to one-half of the posterior lobe of the ox-gland—causes *slowing* of the pulse within two minutes which usually passes off in 7 or 8 minutes in cases of Graves' disease. In normal subjects the pulse is *accelerated* by this injection within two minutes, attains to its maximum in 5 or 6 minutes, and returns to normal within 15 minutes. The originators of this test—Bandouin and Parak—consider that the reaction is indicative of an excess of thyroid secretion in the blood.—R. McC.

vessels, may be found on post-mortem examination as well as lesions due to previous rheumatic attacks.

3. The want of tone in the peripheral vessels is responsible for the flushed skin which is such a common feature, for the attacks of blushing, for the subjective sensations of heat and for the discomfort in hot weather, for the relief by cold weather or cold sponging, as well as for the greatly increased, and often paroxysmal, activity of the sweat glands. The skin is moist and its electrical excitability is thus increased (Charcot). Irregular rises of temperature may be due in some measure to this cause but are in greater measure the effect of increased metabolism. The skin is very sensitive to rubbing and scratching so that local erythema, or degrees of dermographia may be easily produced. Pruritus is common.

The temperature which so frequently follows operation in the subjects of this disease (it is by no means confined to cases where the operation is upon the thyroid) bears no relationship to the severity of the thyroid hyperplasia (Marine and Lenhart).

4. With the increased excitability of the sympathetic nervous system is included an increased activity of the adrenals since the adrenalin-cells and the sympathetic nerves belong to a common system (Elliot). The first duty of the adrenal-sympathetic system is to sustain the activity of the circulatory muscles, consequently its continued excitation leads to alterations of the blood-pressure and to vaso-motor disturbances. Blood-pressure observations have not been recorded on a sufficiently accurate and extensive scale in this disease to justify any definite pronouncement with regard to it. My own experience is that the systolic pressure is in many cases slightly raised, in some cases distinctly so. In other cases it may be normal or slightly below normal, depending largely on the state of the heart-muscle and the degree of peripheral dilatation, and probably also on the presence in the blood-stream of the depressor substances to which previous reference has been made.

It is to the sustained excitation of the adrenal-sympathetic system that the characteristic "frightened facies" and exophthalmos is due (Maurice, Cannon). The occurrence of extensive

pigmentation of the skin justifies the assumption that the adrenals may ultimately be injured, and actual atrophic changes in these organs have been observed by Ratmann. Glycosuria occurs easily.

5. The great increase in the vaso-motor excitability gives rise to prominent symptoms. Thus there is persistent pulsation of the large vessels, the carotid, the abdominal aorta, the iliac arteries as well as of the superficial arteries. This is often a feature which greatly adds to the patient's discomfort. The sphygmographic features of the pulse resemble those of aortic regurgitation (James Mackenzie) : they are " a high upstroke and a rapid fall so that the dicrotic notch is near the base line." The pulse may, however, vary considerably in proportion to the degree of insufficiency of the cardiac muscle.

A capillary pulse may be present and pulsation may occur in the liver and spleen.

The excitation of the autonomous nerves is a prominent feature. Thus the disturbances of the respiratory rhythm, the salivation, the diarrhœa and vomiting which are often early symptoms are attributed by Eppinger and Hess to this cause ; other factors, however, have a bearing on their production.

The progress of the disease leads to a gradually increasing state of exhaustion of the central nervous system which evidences itself in various nervous and mental derangements.

The Mental State.—In many cases the earliest signs of the disease are exhibited by feelings of unrest, anxiety, or apparently uncalled-for apprehension. There is a loss of mental balance. The patient may suffer from headache, sleeplessness, irritability ; she is generally quarrelsome and difficult. Mental fatigue occurs on slight effort, or there is loss of memory or symptoms pointing to a state of neurasthenia. The patient's character always becomes altered. She is emotional and ready to cry for no reason. She may be excited or more rarely depressed, or these states of excitation and depression may alternate. As the disease progresses the excitement or depression may advance to extreme degrees. Actual mania, melancholia or dementia occur

in some cases. Visual or auditory hallucinations, delusions of persecution or grandeur may be present, or the patient may exhibit suicidal or homicidal tendencies. Fortunately these graver evidences of mental derangement are not very common, but their occasional occurrence should be remembered when forming a prognosis.

Metabolic Disturbances.—A notable feature of this malady is the great increase which occurs in all metabolic processes. The respiratory exchanges are stated by Biedl to show an increase of from 50 to 80 per cent. He considers that this increase is due partly to the increased cardiac and respiratory activity, partly to the increased excitation of the nervous system and to the increased activity of all glandular organs, and partly to the motor unrest and tremor. The increased expenditure of energy results in emaciation which is often extreme and is a feature of the disease in the vast majority of cases. The increased heat-production is in part responsible for the subjective sensations of heat and for the irregular increases of body temperature. It is to be remembered, however, that tuberculosis may be associated with this malady.

There is a greatly increased consumption of proteid: the total nitrogen, urea, uric acid, as well as the output of phosphates being increased. The assimilation of carbohydrates is diminished, and alimentary glycosuria and chyluria (Szel) are likely to arise; fat absorption is impaired.

There is a great loss of water while the metabolism of salts, phosphorus, calcium, sodium, and magnesium is increased.

The kidneys are rarely severely affected. Polyuria is common, but in some cases the urine may be scanty. True diabetes may occur, due to organic changes in the pancreas.

Notable changes may occur in the bones, especially in the young, leading to a state of decalcification and softening. When the disease is acquired in early life the skeleton may remain slender. There is an increased vascularity of the periosteum and widening of the Haversian capillaries (Marine and Lenhart, Fuchs). Osteomalacia, arising during the course of Graves' disease, has been

described by v. Recklinghausen and others. I have noticed that the crowns of the teeth are apt to be worn away in a considerable number of cases.

The introduction by American physicians of clinical calorimetry should aid greatly in the study of the metabolic changes in this malady. The Sage calorimeter appears, from the reports of its efficiency which are becoming increasingly common in the literature of American medical science, to be a most convenient apparatus for clinical calorimetric observations in hospitals and research institutions. Observations on the heat-production provide the most certain means of judging of the effects of treatment as well as of the severity of the disease (Du Bois).

With the progress of the malady and the onset of fibrotic changes in the thyroid gland, evidences of impaired metabolism begin to manifest themselves. The patient may gain in weight owing to myxœdematous deposits in various parts of the body. Infiltration of the eyelids may occur or circumscribed areas of œdema in other parts. A solid œdema of the extremities is not uncommon. The skin commences to exhibit evidences of malnutrition and from being moist it becomes dry. Sclerodermia is not infrequent at this stage (v. Leube). The hair which was glossy may fall out or lose its lustre, recede from the forehead and become prematurely grey. The eyelashes and eyebrows may be lost in whole or in part. Pigmentation of the skin is frequent and is often most marked on the eyelids, about the nipples, on exposed parts of the body or where it is subjected to pressure by waistbands or garters. It may give the appearance of sunburn to the face or it may be so marked as to simulate Addison's disease, and indeed in some cases is due to adrenal changes. Leucodermia is comparatively frequent. These minor manifestations of thyroidal atrophy and fibrosis may give place ultimately to the grosser signs of unmistakable myxœdema. According to Granger the cycle from thyroid hyperplasia and excessive action to fibrosis and thyroid deficiency occupies on the average about six years.

Voluntary and Involuntary Muscles.—The fourth cardinal

sign of Graves' disease is tremor. It may be fine and be manifest only in the fingers. It is rapid and rhythmic in character, occurring 8 to 10 times in a second. It should not be confused with the tremor of alcoholism or tobacco-poisoning which it resembles. More rarely it may be coarse in character and amount to an actual shaking of the limbs or even of the head and body, simulating early paralysis agitans. Tremor is present in the great majority of cases, but it may disappear and reappear from time to time. Muscular weakness may be profound. A "giving way of the legs," especially when going upstairs, is a common symptom. The patient is easily fatigued. Arkanazy has found fatty degeneration and atrophy of the muscle-fibres with loss of normal striation in the muscular tissues of the thorax, the abdomen, the pelvis, the eyes, and tongue, which he considers are of toxic origin, and that these changes are comparable to the fatty metamorphosis seen in progressive muscular dystrophy. The respiratory muscles, the diaphragm, as well as the musculature of the heart and intestines, may be involved in the same way. It is stated that this muscular weakness may be present without any great loss in muscle bulk.

The Respiratory System.—The respiratory rhythm is increased, due in part to increased autonomous irritation and possibly also to the action of toxic substances produced in the thyroid gland (Gley). The weakened condition of the respiratory muscles may cause feeble expansion of the chest during inspiration (*Litten's sign*), and imperfect contraction of the diaphragm. Dyspnœa is a common complaint which may be due in part to the above causes or to pressure of the thyroid gland on the trachea. It is frequently paroxysmal and may simulate asthma.

A dry ringing cough is not uncommon; the voice may be hoarse or aphonia may be present. A condition of bronchorrhœa has been described by Murray, and compared by him to the diarrhœa which is frequently associated with this disease and thought by many to be due to vagal irritation.

The Digestive System.—While some of the symptoms referable to this system are undoubtedly due to autonomous

irritation it is to be remembered that alimentary tract poisons are likely to be the most common source of such irritation. A condition of hypo-acidity of the gastric contents is the rule in this malady, and this in itself favours the infection of the upper parts of the alimentary tract by micro-organisms of disease. The frequency with which such disorders of this tract precede the onset of Graves' disease is becoming increasingly evident with the more careful study of the patient's history. Thus Müller reports twenty-four cases in whom achylia was constant in all, and emphasizes the fact that in these there was a condition of chronic gastritis which in some, he was definitely able to show, preceded the Graves' disease. Dilatation of the stomach is also a very frequent accompaniment of the malady, while not a few cases have been reported where it has had its onset in attacks of vomiting and diarrhœa. Curschmann considered that the diarrhœa which was present in 50 per cent. of his cases was due to intestinal toxæmia. Without reliable Röntgen-ray observations, however, it is impossible to state how far the gastric and intestinal disorders are due to stasis of various parts of the alimentary tract. There can be little doubt that such examination as a routine procedure, especially where the screen method is employed, would reveal an ever-increasing number of intestinal toxæmic cases.

Of great interest in this connexion are the post-mortem findings in the liver. This organ "frequently shows some degree of fatty degeneration, while cirrhosis is found in a significant number of cases" (Marine and Lenhart). These evidences of toxic action on this organ are of great importance. The disturbances of fat absorption which occur, and the fact that true diabetes is not uncommonly associated with it, indicate the existence of pancreatic changes; Mutch and Jordan have drawn attention to the rôle of intestinal stasis in the production of such changes.

The appetite is usually abnormal and capricious; anorexia may be present; more commonly the appetite is voracious. Thirst is often complained of. The activity of the salivary glands is usually increased and salivation may be paroxysmal; in other cases the saliva may be scanty.

Paroxysmal vomiting and diarrhœa are not uncommon and as many as 20 to 30 loose, painless, choleraic motions may be passed in one day. Blood may even appear in the stools during such attacks. Between the attacks of diarrhœa the patients are usually constipated.

Having regard to the almost constant presence of gastric hypo-acidity, to the favouring influence which this condition provides for the development of gastro-intestinal infection from the mouth, gums, throat and nose; to the frequency with which gastro-intestinal disorders may precede the disease and accompany it; to the known effects of nutritional disturbances of gastro-intestinal origin on the thyroid gland; to the profound influence which toxins of gastro-intestinal origin are capable of exercising on this organ; to the effects of the products of anaërobic organisms flourishing in this situation, which are similar to those caused by sympathetic excitation; and, to the changes which occur in the liver, the thymus, the pancreas, the adrenals, the muscles, the sympathetic system, and the blood, all of which indicate continued toxic irritation, more attention should be paid to the gastro-intestinal aspect of the malady's ætiology.

The extraordinary results, which followed gastro-enterostomy in the case previously referred to, indicate at least that the thorough examination of the gastro-intestinal tract by every means at our disposal should be more constantly practised in this disease. The correction of any abnormal states which may be found therein, by surgical means if necessary, is a measure which will commend itself to those whose views as to the thyrogenic origin of the malady are not too deep-rooted.

The Sex Organs.—The changes produced in these organs are exemplified in women by the marked alterations which occur in the menstrual function. This function varies with the degree of anæmia present and with the state of general nutrition. It may be greatly disordered resulting in amenorrhœa or menorrhagia; it is only in severe cases that it is wholly suppressed. The mammæ even in emaciated women are often firm and well-shaped. It is stated that circumscribed œdema of the mammæ may occur

in the later stages of the disease. Atrophy of the ovary or of the uterus is rare. Pelvic and sexual disturbances apart from the disorders of menstruation above mentioned are often associated with this condition (Porter). In married women some sort of sexual incompatibility with their husbands is frequent (Thomas). Elsner calls attention to the large proportion of uterine growths which may be associated with it.

Opinions differ as to the effects of pregnancy in this disease. Many writers, especially German, strongly urge its dangers. These are certainly considerable in advanced grades of the malady, but where it is of milder degree or shows signs of improving, it is probably beneficial to the patient. As I have previously pointed out, however, the children of women who are the subjects of Graves' disease are frequently degenerate in some degree.

Loss of sexual power in males occurs occasionally, while rare cases of abnormal development of the mammary glands in the male have been reported.

Our consideration of the morbid changes met with in Graves' disease will have brought into prominence the fact that they are indicative of toxic action. The lymphocytosis, the lymphatic hyperplasia, the lymphocytic infiltration of the thyroid, the liver and other organs; the chronic toxic inflammatory changes in the thyroid, liver and pancreas; the changes in the muscles, in the nervous system and in the adrenals; all these point to a condition of chronic toxic irritation as the underlying factor in their production, and to the gastro-intestinal tract as the most common source of the toxic irritant.

Course and Prognosis.—The course of Graves' disease is very variable. In its beginnings it may appear suddenly as after shock, injury, or some superlative physical and mental exertion. More commonly its onset is gradual in persons who may have appeared to be in good health up to the time of its first appearance. The symptoms may at this early stage disappear for a time or be only very slight, but reappear later with greater vigour. They are more marked at the menstrual periods and exacer-

bations commonly occur in women at the menopause. They are aggravated by attacks of acute illness, "colds," influenza and the like, by physical fatigue, but more especially by psychic excitation. These exacerbations usually subside with their cause but the patient is left the worse for their occurrence. In a large proportion of all cases the patient is capable of attending to her duties, but the more the subject of the disease taxes her nervous and physical resources the worse the symptoms become. After persisting for a year or two the symptoms may more or less completely disappear, especially if the patient is of the leisured classes and able to conserve her energies. There is, however, as a rule, some residuum of the disease left behind in the shape of slight prominence of the eyes, some degree of thyroid enlargement, or of nervousness or uncertainty of temper. In some cases after apparent recovery, whether brought about spontaneously or by rest or surgical means, the symptoms may reappear following some acute illness, severe accident or shock. Fig. 77 shows such a case of recurrence after operation.

With rest and ordinary medical attention it may reasonably be expected that at least 50 per cent. of all cases will eventually recover to the extent of being capable of fulfilling their daily duties more or less efficiently. Thus of 3,523 cases so treated, of which I have been able to find records in the literature, recovery is stated to have occurred in just over 50 per cent.; in 38·5 per cent. of cases the condition had been alleviated or become chronic; while death had resulted from the disease itself in 11·8 per cent. In fatal cases death usually occurs within a period of six months to six years after the onset of the malady; in over 50 per cent. it occurs within eighteen months (Hector Mackenzie). Death is commonly due to cardiac failure, to general exhaustion precipitated by gastro-intestinal crises, and to pneumonia and tuberculosis.

It is only in the milder cases that recovery can be expected to occur. Very rarely more severe cases may attain to a state of health approaching normal, but as a rule such cases either die from the causes above mentioned, or the disease may persist for years, the patients becoming more and more cachectic and the evidences of thyroid impairment more marked. Relapses after

apparent cure by medical means occur in about 20 per cent. of cases.

The prognosis is a matter of great difficulty. It depends primarily on the duration of the disease, on the state of nutrition of the patient, on the extent to which nutrition can be maintained and on how far her position in life permits the conservation of her physical and mental resources. Gastro-intestinal disturbances are of grave import, as is icterus and other evidence of derangement of the liver. In this fact also we have another indication for the desirability of determining the true cause of these disturbances. Prognosis depends also to a large extent on the degree of cardio-vascular disturbance ; on the degree also of lymphatic and thyroid hyperplasia as determined by the estimation of the lymphocytic content of the blood ; on the presence of psychic derangements ; and on continued fever, which usually means death.

The accurate estimation of the degree of metabolic disturbance by the Sage calorimeter appears to afford the most efficient means of arriving at a prognosis in this malady, as well as of the value of any line of treatment. "Control of the disordered metabolism is the essential requisite in any form of treatment employed. The measurement of the heat-production gives the best index of the severity of the disease. Very severe cases show an increase of 75 per cent. or more above the normal average, severe cases 50 per cent. or more, and moderately severe or mild cases less than 50 per cent., while a few mild and atypical or operation cases may be within normal limits" (Du Bois).[1]

Forms of the Disease—Diagnosis.—It is customary to divide the disease into various clinical forms and to speak of primary or secondary cases according as they may have developed *de novo*, or have been super-imposed on an existing goitre ; as acute or chronic, according to their duration ; as *formes frustes* or incomplete cases, according as they fail to exhibit one or more of the

[1] "Clinical Calorimetry," vol. i. Papers 1–17, 1915–1916 : The Russell Sage Institute of Pathology : Chicago, *Am. Med. Assoc.*, 535, N. Dearborn Street, 1915–1916.

four cardinal signs of the disease. To separate the cases clinically into "vascular goitres," "Basadowized goitres," "Basadowian goitres" and "true Basedow's disease" (after Kocher) or into vago-tonic and sympathetico-tonic cases (after Eppinger and Hess) is to introduce complexities which our knowledge of the malady's ætiology does not warrant. Graves' disease is above all things a condition of heightened excitability of the vegetative nerves accompanied by disordered metabolism and abnormal action of all organs innervated by them; of the heart, thyroid and adrenals amongst others, but there is no sufficient justification for classifying all cases in terms of thyroid enlargement. The presence of a goitre exhibiting vascular anomalies in association with other evidences of sympathetic irritation and metabolic disturbances leaves no room for doubt as to the diagnosis, nor does the absence of a goitre where sympathetic and metabolic disturbances are marked. But the presence of a goitre with tachycardia alone, or with tremor alone, is not a sufficient ground for the diagnosis of Graves' disease in the absence of other signs of sympathetic or metabolic disorder. Yet there is abundant evidence from the literature that such cases frequently come to operation. Difficulties only arise where it is sought to establish a diagnosis on the presence or absence of the four cardinal signs of the disease alone; but the recognition of the fact that Graves' disease is a sympathetic and metabolic disorder, and the routine examination by every means at our disposal of all systems of the body will enable a diagnosis to be reached with certainty and without confusion.

As a rule the diagnosis is easy, far easier than in most diseases. It is to be remembered that Graves' disease may exist with any form of goitre—simple hypertrophic, colloid, adenomatous or cystic —but that a vascular and probably painful enlargement of the thyroid is much the most common. The presence of a murmur over the gland, which occurs in 80 to 90 per cent. of all cases, is a valuable diagnostic sign, and where such a murmur is present a careful examination should be made for other symptoms. Very significant also is a history of loss of weight and dyspnœa, while the rapid and rhythmic character of the tremor is of great importance

and should not be confused with that of alcoholism or tobacco-poisoning. I have seen cases diagnosed as Graves' disease in young soldiers in whom simple toxæmic goitres of intestinal origin have been associated with tobacco-poisoning—tachycardia and tremor.

A diagnosis has also to be made from cases of simple goitre with pressure effects on the sympathetic and pneumogastric nerves (so-called false Graves' disease), from cases of orbital tumour, and aneurism of the orbital arteries, from neurasthenia, from cases of hysterical tremor with accelerated cardiac rhythm, and from "iodism," which may be evidenced by palpitation, psychic excitation, nervousness and slight emaciation; in the last case the history will clear up the diagnosis. A much more common error than is generally supposed is a confusion between early Graves' disease and early Parkinson's disease. To the superficial observer, and even to the careful, paralysis agitans is not unlike exophthalmic goitre.

INFLUENCE OF THYROID FEEDING ON ANIMALS AND MAN

Mention has been made of the fact that thyroid feeding in excess cannot give rise to symptoms even remotely resembling Graves' disease in animals. It is necessary, therefore, to give the conclusions of Carlson, Rooks and McKee, whose researches in this direction are amongst the most painstaking with which I am acquainted. They find—

(1) That toxic symptoms can be produced in animals by thyroid feeding; great variations in resistance to thyroid substance are shown by different animals.

(2) In resistant animals the symptoms produced are due partly to large excess of proteid given as thyroid substance.

(3) When thyroid substance is administered in toxic quantities the symptoms produced are loss of weight, gastro-enteritis and diarrhœa.

(4) Thyroid feeding in distinctly toxic quantities does not affect the pulse, nor does the feeding result in

nervousness or exophthalmos in any class of animals experimented upon.

(5) The symptoms can and may be an expression of hyperthyroidism; they are not the true symptoms of Graves' disease.

(6) Man is very much more susceptible to thyroid feeding than other species, therefore the expression of hyperthyroidism in man and in the lower animals may differ. This point is not yet settled, except in so far as to show that experimental hyperthyroidism in animals is not identical with exophthalmic goitre.

With regard to thyroid feeding in excess to man Biedl has concluded that although it may produce increase in the pulse-rate, increased metabolism and increased nervous irritability yet it cannot produce the clinical picture of Graves' disease. With this conclusion most observers are in accord.

Again, while Kendall's α-iodine when administered to animals in excess will produce toxic symptoms simulating exophthalmic goitre, yet it does not give rise to the full clinical picture of Graves' disease. Such symptoms as it causes may be regarded as manifestations of hyperthyroidism, but these apparently do not appear without the chemical intervention of certain amino-acids or of their products. It is highly improbable, also, that the administration of this substance will produce the pathological changes in the various organs and tissues of the body which are found in Graves' disease; indeed, so far as the changes in the sympathetic system are concerned, these do not occur in the state which results from the injection of α-iodine.

It is thus of importance to distinguish between the terms Graves' disease and hyperthyroidism: they are not synonymous, and should not be loosely used. There is no sufficient evidence, either from experiments on animals or observations on man, that hyperthyroidism, that is to say, excess of the *normal* secretion of the thyroid gland, is the direct cause either of the tachycardia, nervousness or exophthalmos which characterize Graves' disease. The symptoms of true hyperthyroidism are loss of weight, gastro-enteritis, diarrhœa, and an increase in the pulse-rate proportionate

to the increase in metabolism. My own view is that under pathological conditions the system is rarely flooded with a chemically unaltered secretion, but that the bio-chemical balance of the secretion may be so changed as to render it deficient in some respect or to impart to it a toxic quality. In the vast majority of cases the excitation which determines the gland's derangement is toxic, and is one which initiates disturbances of the whole endocrine system. This state is something more than mere excess of the thyroid's function. It is the state to which the designation Graves' disease may properly be applied in contradistinction to the more restricted one of hyperthyroidism.

RÔLE OF THE THYROID GLAND IN GRAVES' DISEASE

It remains now to consider the evidences which point to impairment of the thyroid's function arising during the course of Graves' disease. These are (1) atrophic disturbances of the skin and its appendages to which previous reference has been made. (2) The leucocytic changes in the blood which occur also in myxœdema and in cachexia thyreopriva ; the administration of thyroid substance will restore the leucocytic relations to normal in myxœdema while in Graves' disease the theoretical excess of thyroid secretion is supposed to be the cause of their disturbance—a paradox which the thyrogenic theory of the malady does not explain. (3) The emaciation of Graves' disease is comparable at least to that of thyroid deficiency: "The typical, and in my experience invariable, result of suppression of the thyroid's function in adult animals is progressive emaciation which increases to pronounced cachexia and culminates in death" (Biedl). (4) The nervousness and tremor which occur in Graves' disease have also been observed in the early stages of myxœdema by Horsley, and the question arises as to whether in both cases they may not be evidences of thyroid defect. Tetany also, and other grave manifestations of organic change in the central nervous system which are frequent accompaniments of thyroid deficiency may also accompany Graves' disease. (5) The lymphoid changes may be regarded as evidence as much of thyroid defect as of thyroid

hyperactivity since similar changes occur in myxœdema ; and the lymphatic infiltration of the hyperplastic thyroid may be evidenced also in a marked degree in the atrophic organ of myxœdema (Mott). In both cases the lymphatic changes are due to the same cause—toxic irritation. (6) The atrophy of the sex organs is another manifestation of thyroidal disintegration. (7) The histopathological process in Graves' disease and in myxœdema is the same in kind if not in degree: hyperplasia—cell-death—atrophy and fibrosis. (8) The enfeebled resistance of sufferers from Graves' disease to infective agencies may be regarded as evidence of thyroid impairment, since lessening of the bacterial alexines occurs in this disease as well as in myxœdema although thyroid feeding to healthy animals is capable of causing their increase (Fassin and Marbé). (9) Finally, the syndrome of unmistakable myxœdema may be frankly superimposed on that of Graves' disease in its later stages as a natural sequel to the thyroid's exhaustion, and this without causing the disappearance of the characteristic features of the latter malady.

It is true that the subjective and symptomatic manifestations of Graves' disease in its earlier stages present an extraordinary contrast to those of fully developed myxœdema—the one being the antithesis of the other, as Kocher has shown in a table of symptoms which is frequently referred to in text-books on this subject. But here a comparison has been instituted between the earliest evidences of an organ's pathological state and the end-results of that state. A similar comparison might be instituted in the case of morbid derangement of any organ of the body without being nearer to the elucidation of the *cause* of the morbid state. The truth is we must base our conception of the rôle of the thyroid in this disease not on the antithesis of Graves' disease and myxœdema, as evidenced by their symptomatic manifestations, but, on the known pathological and chemical changes which have been abundantly shown to occur in this organ from the very onset of Graves' disease to its ultimate end. The work of Ord, Howard, West, Dock, and especially of Marine and Lenhart has clearly established the relationship of myxœdema to Graves' disease and has shown that the syndrome of the

former is "intimately interwoven with that of the latter throughout its entire course." The accurate histo-pathological work of the last two observers leaves no room for doubt in the matter in the mind of any one who has traced the changes in the thyroid gland from those of active hyperplasia to cell-death and fibrosis in experimentally-produced goitre in rats, and who has thereby been convinced that continued thyroidal hyperaction must finally result in thyroidal atrophy. The demonstration by these observers that neither exophthalmos nor tachycardia bears any definite relationship to the degree of thyroid hyperplasia, the impossibility of producing in animals by excessive thyroid-feeding symptoms which even remotely resemble those of Graves' disease, the fact that such feeding to man himself cannot produce the complete picture of the malady, the super-imposition of the syndrome of myxœdema upon it as its natural sequel, are facts which appear to me to render the theory of the thyrogenic *origin* of Graves' disease altogether untenable. True Graves' disease manifests itself in a state of heightened excitability of the whole sympathetic system, and in consequence in a state of heightened activity of all organs under the control of this system. These organs, the heart, the thyroid, the thymus, the adrenals, the liver, are activated to excess and to the ultimate detriment of each. The thyroid cells are eventually exhausted, as is also the heart's muscle ; but in the full vigour of their early excitation they give rise to symptoms proportionate only to their functional powers of response to stimuli. Thus the severity of Graves' disease may be greatest where the thyroid's powers of response are least, or least where the thyroid's powers of response are greatest; in no case do the clinical symptoms bear any definite relationship to the extent of the goitre or of the secreting surface of the organ. It is a view of the malady which argues an extremely narrow vision, to attribute its origin to a derangement of function in any one organ, whose disorder in reality but adds its quota of symptoms to the general complex.

What, then, is the rôle of the thyroid gland in this malady ? It is a rôle to which symptomatic expression is given in proportion to the degree and stage of the morbid change in the gland itself,

and to the degree of chemical change which the excitant of the disease may bring about in its secretion. The initial hyperplasia results in the flooding of the blood-stream with a secretion which at first is excessive in quantity but from the outset is deficient in quality. It is uncertain to what extent the initial increase in quantity makes up for the deficiency in quality ; at all events symptoms which might reasonably be attributed to hyperthyroidism form part of the clinical picture in the majority of cases during the earlier stages of the malady. But as the morbid change proceeds exhaustion of the secreting cells occurs, and normal secretion is produced in gradually diminishing amount. A stage is ultimately reached when the gland's secretion is insufficient for the body needs, and the characteristic symptoms of myxœdema in minor or major degree are added to the clinical picture ; and long before these gross evidences of thyroid insufficiency manifest themselves the finer nutritional changes in the cells which ultimately lead to them are taking place, and doubtless have their symptomatic expression were we but able to detect it.

It is extremely probable that the net result of the quantitative increase and the qualitative decrease of secretion is, even at a comparatively early stage of the disease-process, deficiency in some one or in all its chemical ingredients. Such symptoms, for example, as nervousness, tremor, mental derangements, etc., may be in some measure the consequence of these finer nutritional disturbances in the cells of the nervous system which this deficiency entails, and which our methods of investigation are still powerless to detect.

The changes in the quality and in the quantity of the thyroid's secretion in this disease are primarily the outcome of toxic excitation of the gland itself and of the sympathetic nerves controlling its secretion. Whether or not the secretion is so chemically altered during the course of the morbid process as to acquire a high degree of toxicity is still not proven. But in either event it is the intervention of chemical substances derived from sources outside the thyroid gland which determines the result and imparts to Graves' disease its toxic character. It is, in my view, only by their removal that a cure can be established.

Treatment.—The first thing to realize is that the removal of all possible toxic excitants of the malady constitutes the essential preliminary to, and must be the basis of, all successful treatment. Thus, the treatment of pyorrhœa alveolaris or of septic tonsils, of chronic appendicitis or gall bladder inflammation, the correction of pelvic disorders, the restitution of the normal drainage of the gastro-intestinal tract, the correction of gastric disorders, the use of antisyphilitic medication where the Wassermann reaction is positive, or of anti-rheumatic measures where rheumatism appears to be connected with its origin, may result in considerable amelioration of the patient's condition if not in actual cure of the disease. The thorough study of the individual in each case is thus an essential requisite to successful treatment.

Its further treatment may be considered under the headings: hygienic; electrical; medicinal; bacteriological; serological; and surgical.

Hygienic measures consist in absolute mental rest and quiet, and as complete physical rest as possible. Mental rest can only be secured away from the patient's own home and the scenes of her disablement. It is important to ascertain the source of the patient's mental distress and apprehension where such exist. The spontaneous unburdening of her mind to a trusted hearer may mark the first step towards her cure. Not infrequently there is present a sexual basis for her unhappiness. Rest is the most satisfactory method of dealing with this disease yet known to us. It reduces the abnormal processes of metabolism like nothing else and without its aid all forms of treatment will almost certainly fail. A dry, cool, bracing, inland climate in the country, where the patient lives in the open air by day and night, is the ideal to be sought for. Daily baths or shower baths, at the patient's body temperature, or colder if these are grateful to her, or hot baths at night to promote sleep are useful, the latter especially where there is restlessness and mental excitability. Massage not carried to the point of fatigue, and, later, gentle walking exercise—where improvement has commenced. A plain, abundant, nutritious diet without unnecessary "sugar and spice," and including very little meat; plenty of green vegetables, fresh

fruits, fresh milk, buttermilk, butter and cream; plenty of hot water between meals and no fluid with meals; a pint of "soured" milk every morning at breakfast; tea and coffee rarely, and very diluted; alcohol never; these are the essentials of the dietary. A daily evacuation of the bowels, secured if necessary by Carlsbad salts in the morning or by paraffin, is a necessity. The patient's weight is the best index of progress. I am of opinion that it is only by the rigid enforcing of these measures that success in treatment is to be attained. They should be commenced at the earliest possible moment in all cases and continued until Nature has effected her cure. It is half-measures in these directions which are responsible for cases hanging on without improvement and often with retrogression.

Electrical treatment includes the application to the thyroid gland of static, galvanic, or faradic currents, all of which appear to be of doubtful efficacy. It is probable that any beneficial action they may possess is due to suggestion, and since suggestion is of value they may be employed to this end.

The Röntgen-ray treatment of the thyroid gland in this disease has come into considerable vogue during the past few years. Reports as to its effects vary greatly. It appears to yield results similar to those of all forms of treatment at present known to us: viz. mild cases may be benefited, severe cases not at all. This treatment has also been applied to the ovaries with results which are reported by its advocates to be as definite as those obtained when it is applied to the thyroid. Thus, Mannaberg [1] considers "that in cases of moderate severity irradiation of the ovaries yields more certain and rapid effects than the measures customarily employed." It has also been applied to the thymus and sometimes affords considerable relief (Simpson).

The same treatment directed towards influencing the adrenals may lead to beneficial results "as these organs appear to be more readily influenced than either the thyroid, thymus, or ovaries" (Zimmeru and Cottenot).

Radium emanations have also been reported to yield successful results (Pinch).

[1] *La Semaine Medicale*, June 11, 1913.

The whole question of the value of the Röntgen-ray treatment of Graves' disease is still *sub judice.* No definite changes occur in the thyroid following its use, beyond an increase in the capsular and pericapsular connective tissue (Marine and Lenhart).

With respect to the *medicinal treatment* of Graves' disease it may be said that drugs should be used as little as possible, and then only where there are definite indications for them. Where the history and examination has suggested a rheumatic excitant, the use of aspirin or salicylates, especially salicylate of bismuth, is indicated; where there is a syphilitic history, antisyphilitic remedies—mercury or salvarsan—find their place; and where an intestinal origin is suspected, intestinal antiseptics —salol, β-naphthol, thymol, benzo-naphthol, or calomel—should be employed.

For the hyper-excitability of the nervous system sedatives and hypnotics are often employed. Since the restlessness, nervousness, and insomnia are "due to loss of, or weakened, inhibitory control over the body functions it is not rational therapy to effect this by correspondingly depressing the accelerator mechanism" (Marine and Lenhart). Opiates should not be used as sedatives for this reason, and the bromides of sodium or potassium rarely, and then only as single large doses to achieve a definite and immediate object. The restlessness and sleeplessness will usually yield to hot baths or hot foot baths and the hygienic measures above indicated; failing these, however, a single full dose of bromide may be given at night.

Of salts of bromine, however, the neutral hydro-bromide of quinine has a place by itself. Administered in five grain doses thrice daily it has appeared to me to justify the enthusiasm of some authors for it. It is especially extolled by Jackson and Mead of Boston who recommend its continued use for two years, and in diminished doses after all symptoms have disappeared. Its beneficial effects are likely to be seen within two months, when its continued use is justified. After some weeks' use of this drug the pulse-rate is frequently lessened, the sweating and tremor diminished and the thyroid may have undergone some

decrease in size. It is essential that the drug should be pure. The action of this salt of quinine is probably due as much to its antiseptic and anti-toxic properties as to its sedative effect on the nervous system. The results of this treatment, as given by Jackson and Mead in 55 typical cases in which it was continuously used, are as follows: 42 were cured (no signs or symptoms for two years) or 76 per cent.; seven cases were benefited (signs or symptoms recurring within two years), or 13 per cent.; six cases were unrelieved, or 11 per cent.

Belladonna also has its use as a cardiac and nervous sedative; it may be regarded as an exception to the rule that sedatives generally are harmful. It is useless to employ it with the object of reducing the thyroid secretion. It acts beneficially on the bowels.

Where there is loss of weight calcium and phosphorus are indicated in the form of calcium chloride, 10 grains thrice daily, or of the lactate in single daily doses of 30 grains, and of sodium phosphate in doses up to 60 grains a day.

Paroxysmal vomiting and diarrhœa are best dealt with by simple diet, evacuation of the stomach or intestine by lavage or cathartics, intestinal antiseptics, large oil enemas, and if necessary opium. A toxic excitant for these crises should be sought for; X-ray examination of the gastro-intestinal tract may reveal stagnation in the stomach or intestines, and where such is found it should be corrected by surgical means if necessary.

For the tachycardia and vascular symptoms, rest with the ice-bag over the heart or over the thyroid, where there is much pulsation in this organ, is all that is required. The indication for the use of digitalis is that in all heart affections—cardiac failure. It should not be employed otherwise. Many physicians speak highly of the value of strophanthus, but the indications for its use appear to be no less clear than for digitalis.

Where chlorosis or anæmia exists arsenic should be employed; this drug is also said to possess the property of controlling thyroid hyperplasia (see page 41). Other complications should be dealt with as they arise, on general principles.

With regard to the use of the animal extracts: adrenal,

thymus, ovary, testes, I have been unable to find from the literature that they are of any real value and my own experience has not encouraged me in their use. There are, however, certain indications for the use of thyroid extract, as in cases where signs of myxœdema are beginning to appear, and where the symptoms of Graves' disease have supervened on simple goitre. Then it may be administered in small doses of $\frac{1}{4}$-$\frac{1}{2}$ grain at night. If carefully watched, it will certainly do no harm, and in such cases it may often do good (Marine, Lenhart, Levi). Thyroid extract is contra-indicated in the severe "toxic" cases of the disease. Where there is evidence of pancreatic derangement, as indicated by the disturbance of fat absorption, pancreatin may be used alone or combined with bile salts. The latter are thought to influence favourably the tachycardia and to improve the general symptoms. A chemical substance—tethelin—has lately been isolated by Robertson from the anterior lobe of the pituitary body which seems, from the very limited number of reports of its use that have so far appeared in the literature, to have an undoubted influence in controlling the tachycardia, nervous manifestations, and disordered metabolism. Richter recommends fifteen to forty grains daily as a suitable dosage. Pituitrin is of value in cases exhibiting pronounced toxic symptoms (Pal).

It is my practice to use the red iodide of mercury ointment—suitably diluted to avoid undue irritation of delicate skins—as an application over the thyroid. I have not employed iodine internally, but having regard to the warnings against its use it is interesting to quote the following passage from a paper by Marine and Lenhart: "We have carefully followed the use of iodine in seventeen cases and have not seen any of the injurious effects commonly described. (Kocher has recently set forth at length the untoward effects of iodine in exophthalmic goitre. We believe such effects are due to the abuse and not to the physiological use of the drug.) Iodine should be administered by the mouth and preferably in the form of the syrup of the iodide of iron, syrup of hydroiodic acid, and sodium iodide. The initial dose should be small. In extreme cases we have used the syrup of ferrous iodide in doses of 5 minims daily for the first

week, 5 minims twice daily for the second week, and 10 minims twice daily for the third week. In mild cases the initial dose may be 5 or even 10 minims twice daily." Used in this way iodine causes a reversion of the thyroid to the colloid state, an increase in the iodine-content of the gland and a decrease in the blood-supply, all of which are desirable objects to be attained.

The *vaccine and serological treatment* includes the use of vaccines and of certain sera. With regard to vaccines, I have employed, as an experimental therapeutic measure, those prepared from coliform organisms from the bowel in several cases where intestinal toxæmia has been the responsible ætiological factor in the case. Although these attempts have not been wanting in success they are as yet too few to admit of conclusions being drawn from them as to the value of such treatment. It is, however, a step in the right direction and can result only in good. Vaccines have a very definite place in the treatment of all focal infections which may occur in this disease. By the vaccine treatment of such foci the disease itself may be greatly benefited.

The sera employed include (1) the antithyroid serum of Moebius and (2) the thyrolytic serum of Beebe and Rogers; with these may be included Rodagen, or the milk of thyrodectomized goats. There is no evidence from the literature that these are of any specific value. Of 3,000 cases treated by Beebe [1] with his serum 50 per cent. were cured or greatly improved; 30 per cent. were better than before; 17 per cent. were somewhat better or unaltered, and 3 per cent. died. Except in so far as this death-rate is considerably below that which occurs with other forms of treatment, the results correspond to those which may be expected from rest alone. The opinion of those observers who have employed these agents most is that they possess no specific action. It must, however, be admitted that some authors are impressed by the utility of the sera.

With regard to the treatment of Graves' disease by surgical

[1] Beebe: *Monthly Cyclopædia and Medical Bulletin.* New series, xvii., No. 3, 1914.

interference with the thyroid gland there are two questions which demand an unhesitating answer in the affirmative before this treatment can be admitted to be justifiable—

(1) Is "Graves' disease the direct outcome of the flooding of the organism with thyroid substance" as it is stated to be by Biedl ?

(2) Does operative interference with the thyroid gland effect what medical and hygienic treatment cannot do ?

With regard to the first the answer has been given in the preceding pages. It is quite definitely negative.

With regard to the second the answer may be given as follows :

(1) At least 50 per cent. of cases will be cured by ordinary medical means, that is to say, by rest and other hygienic measures efficiently employed ; and 80 per cent. of these will remain permanently cured (Hale White).

(2) Of 1,126 cases operated upon by 26 different surgeons between the years 1896 and 1912 (collected by Klose [1]) the percentage of cures recorded ranged between 14·5 per cent. (MacCosh, 1909) and 93·7 per cent. (A. Kocher, 1907). Since the percentage of deaths in the former operator's cases was 4·6 per cent. and in the latter's 6·3 per cent. we may presume that the operative procedures were equally well executed in both ; yet MacCosh records 14·5 per cent. cured and 72·7 per cent. considerably improved, while A. Kocher records 93·7 per cent. cured, none considerably improved, and 6·3 per cent. deaths.

The average percentage of cures of all these operators put together is 60 per cent. This is not a sufficient improvement on medical treatment to justify an operative mortality which in the hands of twenty-six skilful surgeons ranged from 1·3 per cent. to 30 per cent.

(3) There is no definite proof that the cures effected by surgical means (*i.e.* by hemi-thyroidectomy alone or with ligation of arteries) are more lasting than those effected by medical means [2]

[1] Klose : *Die Basedowsche Krankheit*, Ergebn, d. inn. Med. u. Kinderh. Band X. 1913.

[2] It is interesting to note in connexion with operative procedures on the thyroid gland that Dubois found, as a result of calorimetric observations, ligation of the thyroid arteries caused a distinct rise in metabolism, the duration of which was uncertain, in three out of four cases so examined.—R. McC.

(fig. 77). Indeed it is not possible at present, as Crile [1] has pointed out, to state positively what is the net clinical result of any operative measure.

As judged by these results hemi-thyroidectomy possesses little advantage over medical treatment. It may result in some amelioration of the symptoms but this might reasonably be considered to be due at least in part to the enforced rest in bed, to the nature of the operation—than which no more effective method of securing complete quiet and rest could be devised—to the patient's profound faith in its ultimate success, and to the dietetic and general hygienic care which she receives while in hospital. It is well known that surgeons who have claimed the most conspicuous successes have often been the most rigid in securing preliminary rest and effective after-treatment. It is possible also that any apparent advantage of the one treatment over the other might wholly disappear if in each case operated upon we had a histological report on the state of the portion of thyroid gland removed. In four out of eleven "cures" effected by operation at St. Thomas' Hospital "there was no evidence of Graves' disease found on microscopical examination" (Mackenzie); [2] so that in 36 per cent. of these cases which were classed as "cures" we must admit either an error in diagnosis or conclude that the thyroid gland does not show the usual evidences of Graves' disease in a very much higher proportion of cases than has hitherto been supposed.

As a result of a careful study of the literature of the subject and of my own observations in some of the foremost of surgical clinics I have been convinced that many cases are subjected to partial thyroidectomy which are not cases of Graves' disease. It is very necessary, in my opinion, to offer a protest to the present-day tendency not only to operation in cases of so-called incomplete Graves' disease, but also to the tendency of some surgeons to operate in all early cases as a routine procedure.

If we admit that the thyroid secretion may be rendered highly toxic by means such as its chemical interaction with the toxic products of bacterial activity in other parts of the body,

[1] Crile, *Journ. Am. Med. Assoc.*, 1909, liii, 1675.
[2] Mackenzie, H., Bradshaw Lecture, *Lancet*, Nov. 11, 1916.

—and in the present incomplete state of our knowledge I admit the probability, if not the fact,—then the failure to detect, on the most careful examination, the source of the bacterial toxin may render permissible the removal of the major part of the thyroid on the grounds that thereby the combined thyroid and bacterial poison will be substantially reduced. But such a procedure must be regarded rather as one of expediency than as a scientific measure. The essentially harmful agency is the chemical product of bacterial activity not the essentially beneficial chemical product of the thyroid gland. To sacrifice the latter while failing to detect and destroy the former is a procedure which can only be permissible when its detection is impossible by our most modern methods of examination and its destruction impossible by our most modern methods of treatment. But the practice of operative interference with the thyroid gland in all cases of Graves' disease at sight and without applying all the resources of our art in the detection of its cause, as is now a very common custom, is one which cannot be too strongly deprecated.

There is no reason to doubt but that a sufficiently extensive thyroidectomy such as is practised by Dunhill will mitigate those symptoms which may be due to hyperthyroidism on the one hand, or to perversion of the thyroid's secretion on the other. But we must realize the limitations of such an operation and not seek to credit it with the cure of a malady the cause of which it leaves untouched. Nor should the possibility of the subsequent appearance of thyroid deficiency be overlooked. In the present state of our knowledge such an extensive thyroidectomy may be the best we can do in a small proportion of cases, but if it must be done, let it be done only when all else fails and let its results be recorded with scientific precision.

It is no use swelling the literature with reports of cases "cured" by thyroidectomy without the fullest information concerning each case. We must know the symptoms in detail on which the diagnosis was based, we must know the histological appearances which the portion of thyroid removed presented, we must know the extent to which the metabolism was disordered before operation and the extent to which it was rectified by operation, as

compared with cases of the same gravity not so treated but enjoying the same degree of rest and hygienic care; we must have installed in our great hospitals calorimeters which will make these controlled observations possible; we must know the state of the gastro-intestinal tract as indicated by X-ray, bacteriological and chemical examination; and, finally, we must know the subsequent thyroidal history of each case. It is due to the profession that surgeons who practise this method of treatment should provide this information in every case where thyroidectomy has been performed, and it is due to the profession that the physicians of our great institutions should provide similar information. It is only by such methods that the confusion which surrounds the treatment of this malady can be dispersed and that we can hope to arrive at finality with regard to its ætiology. I am convinced that by the application of these methods of scientific observation the number of cases in which thyroidectomy is performed will become smaller and smaller and that its practice, except in cases which have baffled the most painstaking investigagation, will ultimately be abandoned.

I believe that surgery has a more rational place in the treatment of this disease than that of interference with the thyroid gland, namely, the correction of such conditions as chronic appendicitis, chronic-gall bladder inflammation, chronic septic tonsillitis, gastro-intestinal stagnation or other disorders which may obviously be benefited by it. For of what use would it have been to have removed the major part of the girl's thyroid, whose case we have considered in an earlier part of this section, and to have left her with such a degree of gastric stagnation as X-ray examination revealed? Such an operation might have improved her condition temporarily, but without the correction of the stagnation it could not have restored her to health.

Other measures of a surgical character which are employed in the treatment of this disease are: the injection of boiling water into the thyroid gland (Porter), and the injection of a 25 to 50 per cent. solution of quinine and urea hydrochloride into the gland (Leigh Watson). I have no experience of either of these procedures. The first is one which on *a priori* grounds I would not

recommend. For the second it is claimed only that it relieves the symptoms of hyperthyroidism. It is a procedure which requires skill and is attended with very considerable risk to the patient.

Operations on the thymus have also been undertaken for the cure of this disease. It appears to me that such procedures are open to the same objections as those raised with reference to operations on the thyroid.

In conclusion, I urge the necessity for more careful examination of every case for foci of infection, and the necessity for their early removal. I urge the routine Rontgen-ray examination of the gastro-intestinal tract by the screen method as opposed to that of photography. I urge the necessity for the more thorough adoption of medical and hygienic means of cure. I urge the more thorough study of the individual, and the abandonment of the half-hearted policy of physicians with regard to the management of this malady. It is, I believe, pre-eminently true of Graves' disease that if we seek for sources of infection we shall find them, and if we remove them sufficiently early Nature will remove the Graves' disease.

APPENDIX I

LIST OF THE AUTHOR'S PUBLICATIONS ON GOITRE AND ALLIED SUBJECTS (1906–1916)

1. 1906. "Observations on Endemic Goitre in the Chitral and Gilgit Valleys." *Med. Chir. Trans.*, 1906, lxxxix., pp. 437–470.
2. 1906. "Further observations on Endemic Goitre in the Chitral and Gilgit Valleys." *Lancet*, London, 1906, i. p. 1110.
3. 1908. "Further Researches on the Etiology of Endemic Goitre," *Quarterly Journal of Medicine*, London, 1908–1909, ii., pp. 279–289.
4. 1908. "Observations on Endemic Cretinism in the Chitral and Gilgit Valleys," *Proc. Roy. Soc. Med.*, 1908, ii. (Med. Sec.), pp. 1–31.
5. 1909. "A Summary of Further Researches on the Etiology of Endemic Goitre," *Proc. Roy. Soc.*, London, B., 1909, lxxxi., p. 31.
6. 1909. "Observations on the Amœbæ in the Intestines of persons suffering from Goitre in Gilgit," *Quarterly Journal of Microscopical Science*, 1909, liii., pp. 723–736.
7. 1910–11. "A Summary of Further Experimental Researches on the Etiology of Endemic Goitre," (Second Series), *Proc. Roy. Soc.*, 1910–11, lxxxiii., pp. 335–337.
8. 1911. "Experimental Transmission of Goitre from Man to Animals," *Proc. Roy. Soc.*, London, B., 1911, lxxxiv., pp. 155, 156.
9. 1911. "Further Experimental Researches on the Etiology of Endemic Goitre," *Annals of Tropical Medicine and Parasitology*, 1911, v., pp. 1–14.
10. 1911. "The Experimental Transmission of Goitre from Man to Animals," *Annals of Tropical Medicine and Parasitology*, 1911, v., pp. 187–199, 3 plates.
11. 1911. "Endemic Tetany," *Lancet*, June 10, 1911.
12. 1911. "A Second Series of Experiments dealing with the Transmission of Goitre from Man to Animals," *Annals of Tropical Medicine and Parasitology*, 1911, v., pp. 453–471.

13. 1911. "A Résumé of Researches on Endemic Goitre," *Ind. Med. Gaz.*, 1911, xlvi., pp. 253–260, 1 pt.

14. 1912. "The Vaccine Treatment of Simple Goitre," *Proc. Roy. Soc. Med.*, 1912, v. (Med. Sect.), pp. 37–48.

15. 1913. "The Etiology of Endemic Goitre." (Milroy Lectures, Royal College of Physicians), London, 1913.

16. 1914. "Experimental Researches on the Etiology of Endemic Cretinism, Congenital Goitre, and Congenital Parathyroid Disease," *Indian Jour. Med. Research*, 1914, i., No. 3, pp. 505–522.

17. 1914. "An Enquiry into the Causation of Goitre at the Lawrence Military Asylum, Sanawar," *Indian Jour. Med. Research*, 1914, i., No. 3, pp. 536–588.

18. 1914. "Nervous Cretinism," *Proc. Roy. Soc. Med.* (Sect. Child. Disease), 1914, pp. 157–164.

19. 1914. "The Pathogenesis of Experimentally-Produced Goitre," *Ind. Jour. Med. Research*, 1914, ii., No. 1, pp. 183–226.

20. 1914. "Experimental Researches on the Etiology of Endemic Goitre," (Third Series), *Ind. Jour. Med. Research*, 1914, ii., No. 1, pp. 214–226.

21. 1914. "Contributions to the Study of Experimental Beri-Beri," *Ind. Jour. Med. Research*, 1914, ii., No. 1, pp. 369–374.

22. 1915. "The Distribution of Goitre in India," *Ind. Jour. Med. Research*, 1915, ii., No. 3, pp. 778–790.

23. 1915. "Endemic Goitre," *The Practitioner*, Jan. 1915, pp. 70–93.

24. 1916. "On the Experimental Production of Congenital Goitre," *Proc. Roy. Soc. London*, 1916, B. lxxxix. p. 322–327, 1 pl.

25. 1916. "The Experimental Production of Congenital Goitre," *Ind. Jour. Med. Research*, 1916, iv., No. 1, pp. 183–189.

APPENDIX II

INFLUENCE OF INTESTINAL ANTISEPTICS ON SIMPLE GOITRE

TABLE I.—SOME OF THE AUTHOR'S ORIGINAL CASES TREATED IN 1906.

Serial No.	Age of patient.	Duration of goitre.	Nature of goitre.	Circumference of neck in c.ms.	Drug employed.	Days of treatment.	Circumference after treatment in c.ms.	Remarks.
1	40	3–6 months	Uniform hypertrophy	41½	Thymol	45	37	15 grs. night and morning; cured.
2	24	1 year	Ditto	39	,,	26	36½	Ditto; cured.
3	35	1–2 years	Ditto	38	,,	56	35	Ditto; cured.
4	26	6 months	Ditto	38	,,	20	35½	Ditto; cured.
5	23	9 months	Ditto	39	,,	27	36½	Ditto; cured.
6	28	? years	Ditto, and central adenoma	39	,,	25	38	Improved; tumour unaltered, gland surrounding it shrank considerably.
7	19	3 months	Right lobe chiefly	37	,,	16	36	Owing to small size of goitre and unilateral character of swelling the result was much more evident than the measurements indicate.
8	25	6 months	Uniform hypertrophy	40½	,,	21	38	15 grains, twice daily; cured.
9	18	6 months	Ditto	36½	,,	15	33	Ditto; cured.
10	26	1 year	Ditto	39	,,	17	37½	Ditto; much improved.
11	29	?	5 small tumours in substance	38	,,	14	36½	Ditto; shrinkage of gland around the tumours occurred; tumours themselves unaltered.
12	13	6 months	Right-sided swelling	30½	,,	20	28	Ditto; cured.
13	13	Ditto	Uniform swelling	34	,,	23	31½	Ditto; cured.
14	22	Ditto	Right-sided swelling	36½	,,	16	35	Ditto; cured.
15	21	1 year	Ditto	37	,,	46	36	Ditto; improved.
16	17	Ditto	Uniform swelling	37	,,	23	34½	Ditto; much improved, not wholly disappeared.
17	35	2 months ?	Ditto	42	,,	27	38	Ditto; ditto.
18	29	3 months ?	Ditto	38	,,	17	36	Ditto; ditto.
19	15	6 months	Ditto	36½	,,	20	34	Ditto; cured.
20	27	9 months	Ditto; mainly right-sided	37	,,	22	35	Ditto; ditto.

TABLE I.—SOME OF AUTHOR'S ORIGINAL CASES TREATED IN 1906.—*continued.*

Serial No.	Age of patient.	Duration of goitre.	Nature of goitre.	Circumference of neck in c.ms.	Drug employed.	Days of treatment.	Circumference after treatment in c.ms.	Remarks.
36	22	3 months	Uniform swelling	38	β-naphthol	45	36½	10 grs. night and morning; much improved.
37	23	5 months	Ditto	44	,,	60	40	Ditto; almost complete disappearance.
38	20	3 months	Ditto	37	,,	25	36	Ditto; improved.
39	35	3 months ?	Uniform swelling	38	,,	42	35½	Ditto; greatly improved; patient had troublesome dyspnœa which was quite relieved.
40	25	4 months	Ditto	35½	,,	20	34	Ditto; much improved.
53	21	9 months	Ditto	38	,,	44	35	Ditto; ditto.
51	23	9 months	Ditto	34½	Salol	30	33	Ditto; improved.
52	26	9 months	Ditto	35½	,,	30	34	Ditto; ditto.
42	29	4 years ?	Right-sided swelling	36½	,,	31	35½	Ditto; slight improvement.
57	21	3 months	Ditto	36	,,	24	35	Ditto; improved.

These cases are taken at random from amongst a series of 68 treated under experimental conditions during the year 1906; they represent a fair average of the results which follow treatment by thymol, β-naphthol and salol.

In making measurements of the neck in these cases accuracy was secured by marking the neck in front and behind with a nitrate of silver pencil; measurements were thus always made over the same spot.

TABLE II.—DR. FR. MESSERLI'S CASES. (LAUSANNE, 1916.)[1]

Serial No.	Age of patient.	Duration of goitre.	Nature of goitre.	Circumference of neck in c.ms.	Drug employed.	Days of treatment.	Circumference after treatment.	Remarks.
1	20	10 years	Folliculaire hypertrophique	(*a*) 44·5 (*b*) 41	Benzo-naphthol	24	(*a*) 42·5 (*b*) 38	0·5 gram. of drug 2–3 times a day.
2	20	Many years	Ditto	(*a*) 44	,,	21	(*a*) 38·5	Ditto.
3	20	Ditto	Ditto	(*a*) 40	,,	24	(*a*) 37·5	Ditto.
4	20	2 years	Ditto	(*a*) 44 (*b*) 38	,,	24	(*a*) 39 (*b*) 35·5	Ditto; drug given at first twice a day, then thrice.

[1] Le goitre endemique, Lausanne (Suisse), 1916.

TABLE II.—DR. FR. MESSERLI'S CASES. (LAUSANNE, 1916.)[1]—*continued.*

Serial No.	Age of patient.	Duration of goitre.	Nature of goitre.	Circumference of neck in c.ms.	Drug employed.	Days of treatment.	Circumference after treatment.	Remarks.
5	20	Several years	Folliculaire hypertrophique	(*a*) 46 (*b*) 40	Benzo-naphthol	24	(*a*) 42 (*b*) 36	0·5 gram.; drug given at first twice a day then thrice.
6	20	Many years	Ditto	(*a*) 45·5 (*b*) 40	,,	24	(*a*) 40·5 (*b*) 37·5	Ditto; for first fortnight drug was given thrice a day, then 4 times.
7	20	Ditto	Ditto	(*a*) 43·5 (*b*) 40	,,	24	(*a*) 40·5 (*a*) 37·5	Ditto; drug given at first twice, then thrice a day.
8	20	Ditto	Ditto	(*a*) 45 (*b*) 40	,,	18	(*a*) 42 (*b*) 38	Ditto; drug given thrice daily.
9	20	3–4 years	Ditto	(*a*) 45·5 (*b*) 40	,,	38	(*a*) 41 (*b*) 37·5	Ditto; ditto.
10	19	Many years	Ditto	(*a*) 41 (*b*) 38	,,	33	(*a*) 38·5 (*b*) 36	Ditto; ditto.
11	22	6 years	Ditto	(*a*) 44 (*b*) 39	Thymol	37	(*a*) 40 (*b*) 36·5	0·5 grm. of thymol twice a day.
12	26	1 year	Ditto	(*a*) 44 (*b*) 38·5	,,	34	(*a*) 40 (*b*) 36·5	Ditto.
13	24	3 years	Goitre parenchymateux	(*a*) 45 (*b*) 41	Salol	37	(*a*) 40 (*b*) 37·5	1 grm. of salol a day in two doses.
14	19	1 year	Goitre folliculaire hypertrophique	(*a*) 41 (*b*) 35	,,	37	(*a*) 35·5 (*b*) 34	Ditto.
15	20	Many years	Ditto; avec un noyau	(*a*) 40 (*b*) 38	,,	37	(*a*) 36·5 (*b*) 34	Ditto.
16	19	1 year	Goitre parenchymateux mou	(*a*) 41·5 (*b*) 36	,,	37	(*a*) 38 (*b*) 35	Ditto.
17	21	Many years	Goitre folliculaire hypertrophique	(*a*) 45 (*b*) 41	Creosote	37	(*a*) 40·5 (*b*) 38·5	Pil. creosot 0·05 grm. c. sacchar, thrice daily.
18	20	Ditto	Ditto	(*a*) 41 (*b*) 37 5	Pastilles "laxantes"	34	(*a*) 40 (*b*) 36	Aloes, jalap and rhei, diminution slight.
19	19	2 years	Ditto	(*a*) 45 (*b*) 40	,,	21	(*a*) 41 (*b*) 37	
20	20	12 years	Goitre parenchymateux	(*a*) 46·5 (*b*) 39	Tanno-forme	29	(*a*) 40·5 (*b*) 36·5	1 grm. of tanno-forme morning and evening.
21	20	8 years	Goitre folliculaire hypertrophique c. noyau	(*a*) 46 (*b*) 39	Salol	29	(*a*) 42 (*b*) 36	1 grm. of salol night and morning.
22	20	?	Ditto	(*a*) 44 (*b*) 38	Creosote	30	(*a*) 41 (*b*) 36	0·05 grm. creosote in pill daily.
23	20	11 years	Ditto	(*a*) 43·5 (*b*) 38	,,	8	(*a*) 43 (*b*) 36·5	Only treated for 8 days.
24	20	9 years	Goitre parenchymateux	(*a*) 44 (*b*) 37	Calomel	29	(*a*) 40 (*b*) 36	0·05 grm. of calomel every morning.
25	20	?	Goitre folliculaire hypertrophique	(*a*) 44 (*b*) 38·5	Aloes	8	(*a*) 43 (*b*) 38	One aloes pill night and morning.
26	22	3 years	Goitre parenchymateux	(*a*) 43 (*b*) 38	Pastilles "laxantes"	29	(*a*) 39 (*b*) 35	Given morning and evening.

[1] Le goitre endemique, Lausanne (Suisse), 1916.

TABLE II.—DR. FR. MESSERLI'S CASES. (LAUSANNE, 1916)[1]—*continued.*

Serial No.	Age of patient.	Duration of goitre.	Nature of goitre.	Circumference of neck in c.ms.	Drug employed.	Days of treatment.	Circumference after treatment.	Remarks.
27	20	Many years	Goitre folliculaire hypertrophique	(*a*) 45 (*b*) 40	Pastilles "laxantes"	29	(*a*) 41 (*b*) 37	Given morning and evening.
28	20	Ditto	Parenchymateux	(*a*) 46 (*b*) 41	,,	29	(*a*) 41·5 (*b*) 37·5	Ditto
29	20	1 year	Ditto, avec un noyau	(*a*) 44·5 (*b*) 37	Mag. sulph.	29	(*a*) 38·5 (*b*) 35	2 grms. night and morning; much reduction in size but still considerable swelling.
30	20	Many years	Ditto	(*a*) 43 (*b*) 37·5	Soda sulph.	29	(*a*) 39·5 (*b*) 36	5 grms. every morning in a glass of water.
31	20	Ditto	Goitre folliculaire hypertrophique	(*a*) 44·5 (*b*) 38	Pastilles "laxantes" and salol	29	(*a*) 40 (*b*) 36	1·0 grm. salol in morning, pastille in evening.

[1] Le goitre endemique, Lausanne (Suisse), 1916.

For the purposes of measurement Dr. Messerli used a point at the back of the neck over the seventh cervical spine and in front the superior borders of the anterior extremities of the clavicles. This he calls the "base" measurement, and it is indicated as "(*a*)" in the table. His second measurement, indicated as "(*b*)," was taken over the seventh spine behind, and a point at the level of the cricoid cartilage in front. This second measurement corresponds more closely to that followed by me, and the results given by it are more comparable to those shown in Table I.

Dr. Messerli's observations were also carried out under experimental conditions, the patients being kept under observation for some time prior to the commencement of treatment in order to eliminate any possible error due to spontaneous improvement. His observations and measurements were controlled by Dr. Brennecke of Berne. Messerli shows photographs of the majority of his cases before and after treatment, which indicate that complete disappearance of the goitre or marked diminution in its size was the almost constant result of the treatment.

Since my original experiments in this direction were carried out I have treated some two hundred cases by the intestinal antiseptic method with results which have established its value as a therapeutic measure, and indicated the intimate relationship of the hypertrophied thyroid gland to the gastro-intestinal tract.

APPENDIX III

SCHEDULE OF THE MORE IMPORTANT EPIDEMIOLOGICAL AND EXPERIMENTAL RESEARCHES CARRIED OUT BY THE AUTHOR

(1) 1906. Relationship of an unprotected water-supply to the incidence of Goitre. [1.]

Eight villages are situated on the Gilgit Fan. Of these one is supplied by its own spring and was goitre-free at the time these observations were made. Seven others are situated one above the other on a single stream. A second stream joins the first above the fourth village, thus diluting the first supply with a purer water. The following table shows the incidence of goitre in these seven villages, as determined by house-to-house census in 1906.

Village.	Population.	Houses.	Infected houses.	Per cent. of infected houses.	Per cent. of persons infected in infected houses.	Per cent. of total population goitrous.
1	93	15	9	60·0	21·2	11·8
2	385	66	42	63·6	28·3	20·0
3	181	30	20	66·6	30·3	18·8
4	718	108	68	63·2	24·2	20·0
5	229	33	23	71·5	30·0	26·9
6	458	63	52	82·5	30·0	24·5
7	128	24	21	87·0	36·0	45·6

The percentages of infected houses, of infected individuals in these houses, and of the total population show a steady increase from the village highest to that lowest on the water-supply. There is a slight drop in the incidence of the disease where the stream is diluted by the purer supply.

This finding has been confirmed in detail by the observations of Marine, Lenhart, and Gaylord on artificially-bred trout (1909–1912).

(2) 1906. to 1910. Object of experiment: To produce goitre in man by means of substances extracted from a goitrigenous water. [3, 5, 7, 15.]

These were controlled observations rather than experiments. The water employed was that which the men would have had to consume under ordinary conditions of life.

a. Twelve individuals, of whom I myself was one, were isolated in a non-goitrous area and given every morning in milk a quantity of the residue left on the candle of a Berkefeld filter after filtration of a goitrigenous water. Four developed noticeable swellings of the thyroid gland within 30 days. In another a slight transitory swelling occurred. Six other individuals, of a like age and similarly isolated, to whom the same residue was given after prolonged boiling, showed within 30 days, no appreciable change in the size of the thyroid gland which could be detected clinically.

β. The above experiment was repeated in the autumn of 1907, but in this case the sediment from the goitrigenous water was given night and morning. Of fourteen individuals so treated, of whom I, myself, was one, and who were isolated as above, five, including myself, developed swellings of the thyroid. In three it was transitory and disappeared spontaneously during the course of the experiment. The experiment lasted 30 days.

Fifteen others consumed the same sediment after prolonged boiling, but in none did any enlargement of the gland occur.

γ. The experiment was repeated in 1910, but prolonged over a period of 55 days. Of ten individuals who consumed the untreated residue of a goitrigenous water, four developed a noticeable swelling of the thyroid. One of these is shown in the text, figs. 26 and 27, p. 93. A fifth developed a transitory swelling only.

Ten other individuals who consumed the same residue after prolonged boiling remained free from any thyroid swelling.

Result: (1) Of thirty-six individuals who consumed the untreated suspended matter of a notoriously goitre-producing water, twenty-one exhibited no change in the thyroid gland which could be detected clinically, while ten developed a noticeable enlargement of the organ and five a transitory swelling only.

(2) Of thirty-one individuals who consumed the same suspended matter after it had been boiled, none showed any enlargement of the thyroid gland.

It was shown also by observations on man that the water when

filtered through a Berkefeld filter did not produce swelling of the thyroid gland within a period of 55 days. The young men on whom these observations were made were susceptible new-comers to the goitrous district. Gaylord's experiments on dogs and rats confirm these results (1912).

(3) 1910. Object of the experiment: To convey goitre from man to animals by contaminating their water-supply with the fæces of goitrous persons. [8, 9, 10, 12.]

Goats were employed for these experiments.

α. Thirteen goats consumed a grossly contaminated water for two months. Of these 50 per cent. showed enlargements of the thyroid gland as determined by weight and by comparison with controls fed on the same food, but given pure water.

1911. *β*. The experiment as above was repeated, twelve young female goats being employed. In this case it lasted 108 days. Seven of these animals were killed; in three the thyroid was larger than normal and showed marked hyperplastic changes on microscopical examination.

Result: Nine out of twenty goats, fed for periods of from 60 to 108 days on a water grossly contaminated by the fæces of goitrous persons, developed goitrous changes in the thyroid gland. This finding was confirmed by Sazaki, working under the direction of Professor Wilms of Heidelberg, in 1913 (*Ergebnisse der Chirurgie und Orthopadie*, Bd. v. Berlin, 1913).

(4) 1911. Object of the experiment: To note the effect on the thyroid gland of animals of the daily administration of living cultures from the fæces of goitrous persons. [10, 12.]

α. Seven young female goats were given cultures from the fæces of goitrous individuals daily for a period of 108 days. A spore-bearing organism derived from the fæces of a goitrous horse was largely employed for this purpose.

Result: In five of these animals the thyroid was found to be considerably *smaller* than that of controls, in two of them decidedly so. A marked hyperplasia accompanied this diminution in size in four cases, in one of which it had proceeded to the point of extensive cell-death and fibrosis; the greatly increased weight of this animal as compared with the controls suggested that myxœdema had been produced.

(5) 1913. Object of the experiment: To diminish the incidence of goitre in a large school in the Himalayas by the chemical purification of the water-supply. [17.]

The experiment commenced on the 19th April, 1913, and terminated on the 25th November, 1913.

Bacteriological examination carried out at frequent intervals for four months revealed the presence of *B. coli* in 10 c.c. of water and under in 28 samples out of a total of 32 examined. *B. enteritidis sporogenes* was also found in 20 c.c. of water on 28 occasions. The water was thus shown to be liable to fæcal contamination. (The bacteriological examinations were conducted by Dr. E. C. R. Fox.)

At the commencement of the experiment 57 out of a total of 284 boys in the school were goitrous, 57 out of a total of 216 girls.

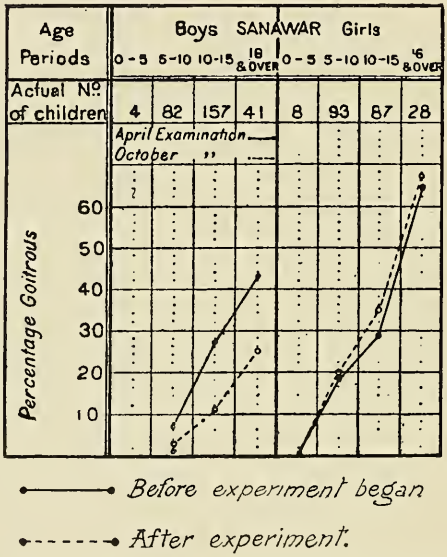


Fig. 78.—Chart showing incidence of goitre in boys and girls at the Lawrence Military Asylum, Sanawar; also the effect of experimental purification of the boys' drinking water.

The experiment consisted in the provision of a chemically purified water to the boys while the untreated water continued to be used by the girls. The purifying reagents were added to the water as follows:

19th April–3rd May: 1½ grains of Nesfield's reagent ($5\,KI.KIO_3$) to the gallon of water.

5th May–10th May: 1 grain to the gallon of ditto.

11th May–2nd July: ½ grain ditto.

3rd July–25th Nov.: ½ grain of calcium hypochlorite to the gallon of water.

This experiment was conducted by Captain M. A. Nicholson, I.M.S., under my direction ; the purification of the water was controlled by repeated bacteriological examinations by Dr. Fox.

Result : The percentage of goitre amongst the boys was reduced by half, while amongst the girls the incidence of the disease increased slightly (fig. 78).

This finding is to be compared with that of Marine, Lenhart and Gaylord in the case of artificially-bred trout, where the addition of iodine, of mercuric chloride, or of arsenic to the tanks in which these fish live suffices to prevent the occurrence of thyroid hyperplasia, and even to cure the goitres from which the fish may suffer.

(6) 1913. Object of the experiment : To convey goitre to rats by feeding them on fæcal material from goitrous persons. [20.]

α. Six white rats were confined in each of three compartments in a single cage. Two were taken at random, as samples of the batch, and killed prior to the commencement of the feeding experiment in order to determine the macroscopical and histological characters of the thyroid. These were normal. The animals in one compartment were given the filtrate of a fæcal emulsion as their only drinking water ; those in another the residue left on the candle of the Berkefeld filter after its filtration ; those in the third compartment acted as controls. The experiment lasted two months. The cage was scalded out with boiling water daily.

Result : 100 per cent. of the animals receiving fæcal material showed large goitres, with marked thyroid hyperplasia on microscopical examination. The controls were normal both macroscopically and microscopically (fig. 32, p. 97).

β. Eight white rats were fed on the fæcal filtrate from goitrous persons for $4\frac{1}{2}$ months. Their cage was scalded out with boiling water daily.

Result : 100 per cent. showed goitrous changes in the thyroid gland ; in some cases massive goitres were produced (fig. 79).

Six control rats fed, in a precisely similar way, but receiving no fæcal filtrate, showed normal thyroids on macroscopical and microscopical examination (fig. 82).

(7) 1913. Object of the experiment : To ascertain the effect of confining white rats for a prolonged period in such a way that their food was fouled by the accumulation of their own excrement. 100 per cent. of white rats so confined showed massive goitres after 6 months. [20.]

(8) 1913. Object of the experiment : To ascertain the effect of feeding white rats on *aërobic* cultures from the fæces of goitrous persons. [20.]

Ten rats were fed on these cultures for $5\frac{1}{2}$ months, their cages being kept as hygienic as possible.

FIG. 79.—Thyroid glands (posterior view, natural size) of white rats fed for a period of $4\frac{1}{2}$ months on the filtrate from fæcal emulsions of goitrous persons. Thyroids of three wild rats shown for comparison. The figures under each gland indicate the sex and weight of the animals in grammes.

Result : 30 per cent. showed massive goitrous enlargement of the thyroid gland (fig. 80). Six control white rats remained normal during this period.

(9) 1913. Object of the experiment: To ascertain the effect of feeding white rats on *anaërobic* cultures from the fæces of goitrous persons. [20.]

Eight white rats were fed on these cultures for $3\frac{1}{2}$ months; their cage being kept as hygienic as possible.

FIG. 80.—Thyroid glands (posterior view, natural size) of rats fed for a period of $4\frac{1}{2}$ months on *aërobic* cultures from fæces of a goitrous person. Three show massive enlargements. The figures indicate the weight of each animal in grammes. The thyroids of five normal animals are shown in the last line.

Result: 100 per cent. showed goitrous enlargement of the thyroid; in six cases the histological appearances were more marked in the direction of fibrotic change than in any others met with in these experiments. The goitres were of comparatively small size (fig. 81). Six control white rats remained normal during this period (fig. 82).

(10) 1913. Object of the experiment: To ascertain the effects on

the offspring of the administration of *fœcal filtrate* from goitrous persons to goitrous female white rats throughout pregnancy. [16.]

Thirty-one young were born during the course of the experiment, which lasted 4½ months. The first litter was born one month after the commencement of the experiment; the young animals were normal in appearance and were allowed to grow to maturity. The second litter of three was born 58 days after the commencement of the experiment, of these one was a cretin (fig. 34). The parents subsequently ate it. The other two were normal in appearance, as were their thyroids on microscopical examination. On the 81st day of the experiment a third litter of seven was born. Of these the parents ate two. The histological appearances of the thyroids and parathyroids of the remaining five were as follows :—

(1) Thyroid: partial hyperplasia, isthmus complete fibrosis (fig. 50). Parathyroids : almost completely destroyed by hæmorrhage into their substance (fig. 69).

(2) Normal thyroid and parathyroids.

(3) Slight hyperplasia of thyroid reverting to the colloid state. Parathyroids normal.

(4) Ditto.

(5) Ditto.

It is extremely difficult to draw the line between the normal and the abnormal in the thyroids of the very young unless the glands are obviously enlarged.

On the 111th day of the experiment a fourth litter of six was born. Of these five appeared to be normal. The sixth was a cretin. Of the five apparently normal young all showed some degree of hyperplasia of the thyroid. The parathyroids were normal in the four cases in which they were found.

On the 142nd day of the experiment a fifth litter of four was born. One of these was a cretin and the thyroid and parathyroids were represented wholly by fibroblasts (fig. 25, p. 75). Of the remaining three two showed normal thyroids, the third showed a certain amount of fibrosis. In all three the fibrous stroma of the parathyroids appeared to be increased at the expense of the parenchyma.

Thus of the seventeen young rats examined in this experiment—

(1) Three were cretins ;

(2) Seven had congenital goitre ;

(3) In seven the glands were normal ;

Five showed changes in the parathyroids of greater or lesser extent.

(11) 1913. Object of the experiment: To determine the ante-natal action of *aërobic* bacteria, grown from the fæces of goitrous persons, on the developing thyroid apparatus. [16.] These cultures were administered to the parents throughout a period of $5\frac{1}{2}$ months. Two female rats gave birth to thirty-five young during the course of this experiment.

The thyroids and parathyroids of ten of these were examined microscopically. All showed pronounced hyperplasia of the thyroid. The parathyroids were found in six cases and were normal.

Control: The goitrous mother of five of these young was subsequently removed to another cage and fed on normal food, no cultures being given. She was impregnated by a goitrous male. After 32 days in the isolation cage she gave birth to seven young. The thyroids of all were normal. The parathyroids of five only were found and these were normal.

Presumably then the previous administration of the *aërobic* cultures did not suffice to cause thyroid hyperplasia in the offspring; that is to say, such organisms (if any) as may have been implanted in the gastro-intestinal tract in consequence of the previous administration of *aërobic* cultures did not suffice to induce goitrous changes in the thyroids of the young conceived after the administration of the cultures had ceased. From this I conclude that it was the toxic substances contained in the culture tubes which induced the thyroid hyperplasias in the offspring in the first instance.

(12) 1913. Object of the experiment: To determine the ante-natal action of *anaërobic* bacteria, grown from the fæces of goitrous persons, on the developing thyroid apparatus [16]. These cultures were administered to the parents throughout a period of $3\frac{1}{2}$ months. Four female rats gave birth to sixty-eight young during the course of the experiment. Nineteen were killed within ten days of birth for examination of the thyroid and parathyroid glands. Result: eleven showed thyroid hyperplasia (congenital goitre) in only one of these was the hyperplasia slight; in the remaining ten it was pronounced; eight showed normal thyroids. The parathyroids were found in sixteen cases. They showed well-marked evidences of disease in eleven cases. The changes consisted in enlargement of the vessels of the glandule, in hæmorrhages which destroyed

large portions of its substance and in more or less extensive fibroblastic invasion. Where an external parathyroid was found (this is not infrequent) it also was diseased in the same way.

Of nineteen cases examined, therefore, ten showed very definite congenital goitre and eleven showed equally definite parathyroid disease.

Control: One goitrous mother was removed to an "isolation" cage. The *anaërobic* cultures were discontinued, and she was impregnated by a goitrous male. After the lapse of 36 days she gave birth to four young. Definite hyperplasia of the thyroid was observed in all; the parathyroids were normal in the two cases in which they were found. *Anaërobes* capable of producing thyroid changes in the offspring had probably been implanted in the intestine of this mother. This result contrasts strikingly with the control to the preceding experiment. In the later case the *aërobes* previously administered to the mother did not suffice to affect the thyroid apparatus of the offspring when their administration was discontinued.

(13) 1914. Object of the experiment: To determine the ante-natal action of fæcal bacteria, grown from the fæces of goitrous persons, on the developing thyroid apparatus of goats [24, 25]. The mothers were fed on cultures of these bacteria throughout a period of $15\frac{1}{2}$ months. Twelve female goats of the first year were confined in a large pen and fed daily on these bacteria. After some months the thyroid glands of all were palpable. They were then impregnated by the same non-goitrous male, and throughout pregnancy were fed daily on *anaërobic* cultures, grown from the fæces of goitrous persons. Eleven kids were born of which one only was born alive. All were born goitrous, the goitres often being of very large size (figs. 33, 53). The ten still-born kids were hairless, macerated, and ill-developed (fig. 33, pp. 98, 121).

Eight female goats of the first year were used as controls. They were isolated one from the other by tethering them to pegs. To avoid as far as possible the contamination of their food by their own excrement four were muzzled, being fed only at stated intervals; four for the sake of comparison were left unmuzzled. Three kids were born to the four muzzled goats, none of which were goitrous, although one was prematurely-born. Two kids were born to the unmuzzled goats of which one was still-born, fully

FIG. 81.—Thyroid glands (posterior view, natural size) of rats fed on *anaërobic* cultures from the fæces of goitrous persons. The thyroids of four wild rats are shown for comparison. The goitrous enlargement was due very largely to the growth of the lobes in a backward direction behind the œsophagus. The figures indicate the weight in grammes of each animal.

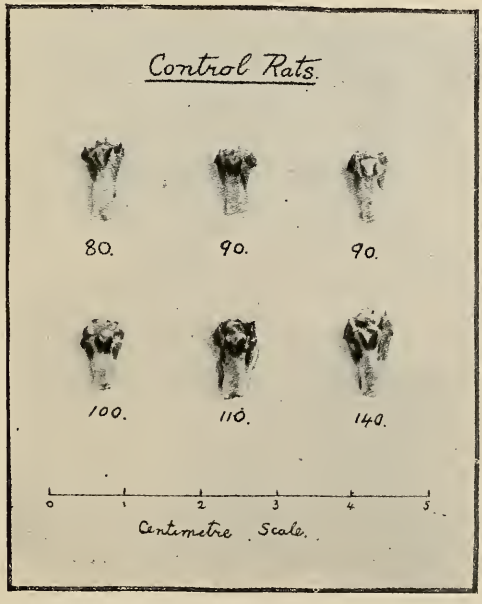


FIG. 82.—Thyroid glands (posterior view, natural size) of control white rats which were kept under experimental conditions for a period of nine months. The figures indicate the weight in grammes of each animal.

developed and with a perfect coat of hair; it had a small enlargement of the thyroid. The second was born alive and perfectly developed in every way, slight enlargement of the thyroid, which disappeared shortly after birth, was present. The mothers of both of these kids had small goitres.

The difference in these results is so striking as to leave no room for doubt as to the noxious effects of the *anaërobic* cultures which were administered. Cultural observations —both aërobic and anaërobic—showed these congenital goitres to be invariably sterile.

(14) 1914. Object of the experiment: To ascertain the possible action of suctorial insects in conveying goitre.

It is unnecessary to give the details of these experiments which were uniformly negative. Suffice it to say that it was found impossible to produce changes in the thyroid glands of dogs by frequent subcutaneous injection of extracts of the mashed-up bodies of lice, bugs, and fleas taken from the bodies, houses or cages of goitrous subjects.

1914. Other negative results of experiments were: (1) the non-production of goitre in rats by mixing their food with the urine of goitrous subjects; (2) the lack of influence of earth worms in spreading the disease; (3) the failure to produce goitre in rats by the daily administration of cultures of *B. coli* or of *streptococci* obtained from goitrigenous water.

INDEX

THE END

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