The Goulstonian lectures on the pathology of the thyroid gland : delivered before the Royal College of Physicians of London / by George R. Murray.

THE GOULSTONIAN LECTURE

1899.

ROYAL COLLEGE OF PHYSICIANS

THE PATHOLOGY OF THE THYROID GLAND

BY

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George Murray

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The Goulstonian Lectures

ON

THE PATHOLOGY OF THE THYROID GLAND

DELIVERED BEFORE

THE ROYAL COLLEGE OF PHYSICIANS OF LONDON

BY

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THE PATHOLOGY OF THE THYROID GLAND.

LECTURE I.[1]

MR. PRESIDENT AND GENTLEMEN,—I must, in the first place, thank you very sincerely for the honour which you have conferred upon me by asking me to deliver the Goulstonian Lectures for this year, an honour which I feel to be all the greater when I read the list of distinguished Fellows of this College who have preceded me in this lectureship in whose footsteps I can but humbly endeavour to follow.

GENERAL SCOPE OF THE LECTURES.

In selecting the subject for these lectures I have been guided by three considerations. First, the widespread interest which has been aroused in the pathology and treatment of diseases of thyroid gland during the last few years. Secondly, the good example which the subject affords of how experimental research in pathology yields results which are of the greatest importance and assistance to the physician in his daily work of treating disease. Thirdly, the opportunity which I have had of devoting some attention to the subject may, I venture to hope, enable me to present it in a manner which will interest you. I shall not attempt to cover the whole ground but shall for the most part deal with those parts of the subject which I have been able to examine for myself, nor will time permit me to allude to all the valuable work which has been done by the many workers in this branch of pathology. I trust, therefore, that this explanation will excuse any omissions which I may make in not referring to the work of others.

It will be convenient first to consider the development and structure of the thyroid gland and the method in which its characteristic secretion is produced. This will clear the way for the consideration of the results

[1] Delivered on March 7th, 1899.

which follow when this function is diminished or lost by removal of the gland in animals or by its destruction by disease in man. The removal of the thyroidal insufficiency thus induced by maintaining a supply of secretion from other sources will be considered as a means of treatment. I propose also to deal with the question of compensatory hypertrophy as illustrated by the thyroid gland, while in conclusion the pathology of exophthalmic goitre will be considered as far as our present knowlege of the subject permits.

Development and Structure of the Thyroid Gland.

The embryology and comparative anatomy of the thyroid gland furnish us with important information as to the origin of its present situation, structure, and function in man. The gland is developed in the embryo in three different parts. A median diverticulum of the hypoblast which lines the pharynx of the embryo is formed between the ventral ends of the second visceral arches, while a lateral diverticulum is developed on each side from the posterior wall of the fourth visceral cleft. In man the median portion persists for a time as a hollow vesicle from which a small canal, the thyreoglossal duct, leads to an opening on the dorsal surface of the tongue. At a later stage this vesicle becomes solid and the duct disappears, while its external opening on the surface of the tongue persists as the foramen cæcum in the adult. The two lateral diverticula fuse with the central portion, forming a mass shaped like a horseshoe encircling the embryonic larynx. All three portions become separated from the hypoblast from which they originated and develop into a mass of branching cell-cylinders. These cell-cylinders are later divided up by the ingrowth of connective tissue containing blood-vessels into separate vesicles. These gradually increase in size and become hollowed out by the accumulation of the colloid substance which is secreted by the epithelial cells into the lumen of the alveolus. His[2] has found that in some cases the thyreoglossal duct already mentioned does not become obliterated, but that it persists in the adult as the lingual duct which has been traced from the foramen cæcum as far down as the hyoid bone. In some cases the middle lobe of the gland is continued upwards as a narrow tube, the thyroid duct, as far as the hyoid bone. The late Professor Kanthack,[3] who examined 100 adults for these ducts, however, found neither a lingual nor a thyroid duct in any of the cases which he investigated and in many there was not even a foramen cæcum. The important fact remains that the thyroid gland is developed primarily as an outgrowth of the pharyngeal hypoblast, and in some lower animals this connexion with the pharynx is still maintained.

[2] Anatomie menschlicher Embryonen.
[3] Journal of Anatomy and Physiology, vol. xxv., p. 155.

Andriezen[4] directed attention to the fact that the thyroid gland is represented in ascidians by a mass of glandular tissue and in amphioxus by a hypobronchial organ which pours its secretion directly into the pharynx. In higher forms (such as fishes) the gland is embedded in the surrounding tissues but the duct which communicates with the pharynx still remains. Thus both the ontogenetic and phylogenetic histories clearly show that the gland as we now find it in man is descended from a secretory gland which originally was provided with a duct through which the secretion passed into the pharynx just as the secretion of the salivary glands still flows into the mouth. In this we find an explanation of the fact that the activity of the thyroid secretion is not destroyed by passage through the stomach but still can produce all its usual physiological effects when swallowed and absorbed from the alimentary canal as it doubtless was by our remote ancestors. This mode of evolution seems to indicate that a ductless gland with an internal secretion is a higher stage of development of a duct gland with an external secretion.

The fully developed gland consists of three parts—two lateral lobes and the isthmus which unites them. The two lobes are closely applied to the sides of the larynx and trachea and extend backwards as far as the sides of the pharynx and œsophagus. At the level of the isthmus the recurrent laryngeal nerve lies in the angle between the œsophagus and the trachea, being covered externally by the lateral lobe of the gland on each side. In front the gland is covered by the sterno-hyoid, the sterno-thyroid, and omo-hyoid muscles. Laterally the lobes extend outwards in front of the common carotid arteries. Each lateral lobe is shaped somewhat like an almond but the upper end is narrower and more pointed than the lower. The lower end lies on the fifth or sixth ring of the trachea, while the upper is generally on a level with the middle of the thyroid cartilage. The position of the isthmus varies, but it generally lies in front of the second, third, and fourth rings of the trachea. In many cases, variously estimated at from 40 to 68 per cent., the pyramid or middle lobe extends as a thin process from the isthmus or from a neighbouring part of one of the lateral lobes up to the hyoid bone to which it is attached by muscular or fibrous tissue. The gland is firmly fixed to the larynx and trachea by fibrous tissue so that it follows the movements of these structures which take place during deglutition. The gland when freshly removed is of a dark red-brown colour. It usually weighs from an ounce to an ounce and a half (from 30 to 50 grammes). It is relatively larger in the infant than in the adult; thus Huschke and Weibgen[5] found that in newly-born children the weight of the gland was equal to from $\frac{1}{400}$ to $\frac{1}{500}$ and in adults from $\frac{1}{1223}$ to $\frac{1}{1800}$ of the total weight of the body.

[4] Brit. Med. Jour., Sept. 23rd, 1893, p. 678.
[5] Münchener Medicinische Abhandlungen, 1891.

The gland is as a rule somewhat larger in women than in men, though Ewald[6] makes a contrary statement supported by Weibgen who gives the average weight in the male as 34·2 grammes, and in the female as 29·3 grammes. Each lobe is about two inches (50 mm.) long, an inch and a quarter (30 mm.) broad, and three quarters of an inch (18 mm.) deep. The right is generally a little larger than the left. The isthmus is about half an inch (12 mm.) broad, and from a quarter to three quarters of an inch deep. The whole gland, however, is liable to considerable variations in structure, such as inequality in size between the two lobes, absence of one lobe, and absence or irregularity of the isthmus. There is a rich blood-supply from four arteries, the superior and the inferior thyroid arteries on each side, and in some cases there is a further supply by the thyroidea ima. These arteries are tortuous and very large for the size of the gland which they supply; they form many anastomoses and finally end in a network of capillaries closely surrounding each alveolus. The capillaries come into close relationship with the epithelial cells and some capillary loops even project between them. The veins which, according to Sappey, have no valves unite to form the superior, middle, and inferior thyroid veins, the two former of which open into the internal jugular vein while the latter enters the innominate. The lymphatics start from the lymph spaces in the connective tissue which surrounds and unites the vesicles of the gland. They unite to form large trunks which freely anastomose both in the substance of the gland and also upon its surface. On leaving the gland the lymphatics pass through the superior and inferior deep cervical glands to join the jugular lymphatic trunk which on the left opens into the thoracic duct and on the right into the right lymphatic duct, each of which discharges into the venous blood-stream at the point where the innominate vein is formed by the junction of the internal jugular and subclavian veins on each side. The nerves which supply the gland come from the middle and inferior cervical sympathetic ganglia and pass into it with the blood-vessels. The nerve branches run in close proximity to the bases of the epithelial cells but the actual nerve-endings have not yet been described.

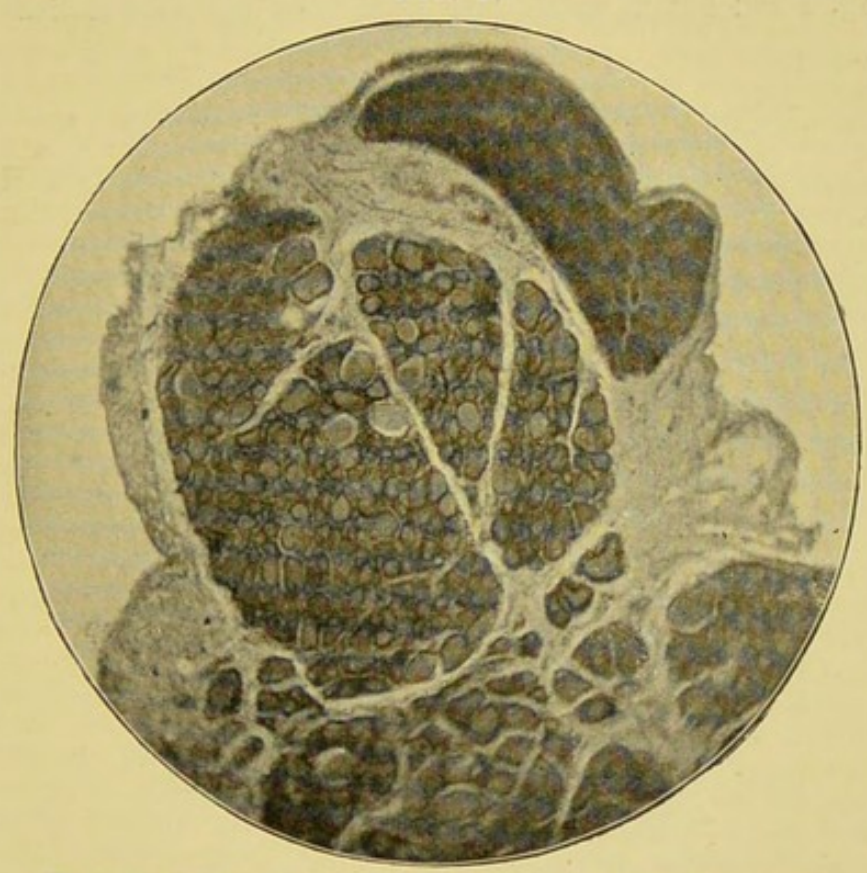
Histology.

Externally the gland is invested by a firm fibrous capsule from which septa extend inwards, partially dividing it into lobules of various sizes. Still finer divisions of this connective tissue framework surround the individual follicles and support the small divisions of the blood-vessels, lymphatics, and nerves. The glandular structure consists of large numbers of closely aggregated follicles which vary in size

[6] Die Erkrankungen der Schilddrüse, p. 3

and shape. On section they appear round, polyhedral, or flattened, and the diameter in man ranges from 0·045 mm. to 1 mm. In the great majority of the follicles there is a single layer of cubical epithelial cells surrounding a central area filled with their secretion, the colloid substance. Some of the follicles seen in a section of the gland appear as masses of cubical cells without any central space. This appearance is in some cases due to one side of the alveolus alone being exposed in the section; in others to the alveolus not being distended

FIG. 1.



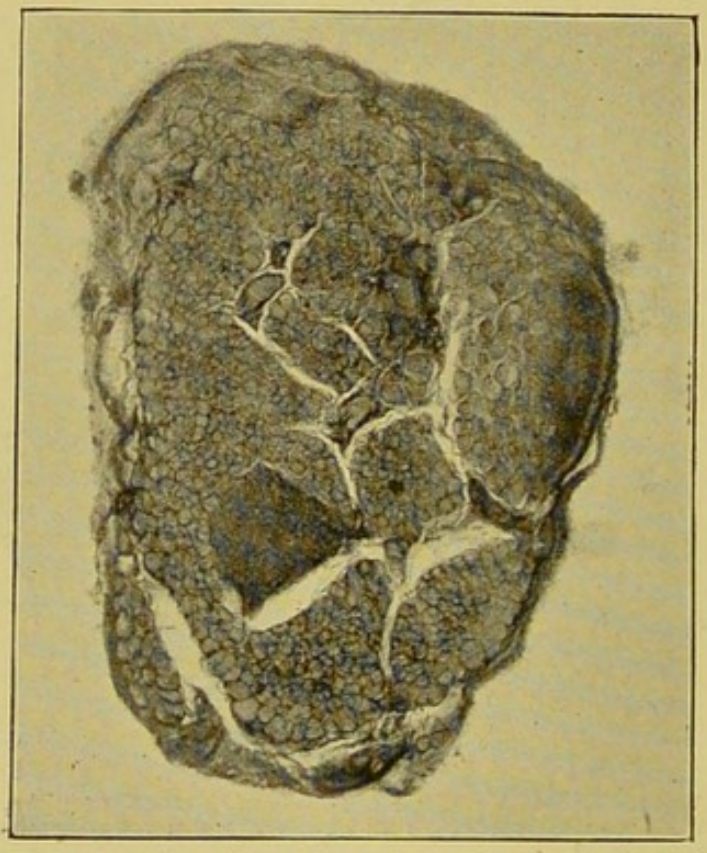
Transverse section of thyroid gland of bonnet monkey, showing general structure and close attachment of parathyroid gland.

with secretion. No basement membrane to the epithelium has been described. Two kinds of cells are found in the epithelium—the chief cells and the colloid cells. The chief cells are usually cylindrical, sometimes cubical, in shape. They measure from 8 μ to 16 μ in height and from 6 μ to 8 μ in breadth, while the nucleus which is round measures from 5 μ to 6 μ in diameter. The colloid cells are considerably shorter than the chief cells, thus Hürthle [7] found in one specimen that while the chief cells measured

[7] Pflüger's Archiv, 1894, vol. lvi. 1.

from 12 μ to 14 μ in height the colloid were only from 7 μ to 9 μ high. The colloid cells are also distinguishable from the chief cells by the readiness with which they take up those staining fluids which also stain the colloid substance in the centre of the follicle. Intermediate types may also be observed. The colloid substance which occupies the central space of the alveolus is a yellow glairy fluid which stains uniformly in microscopical sections. Scattered through it may sometimes be seen white blood corpuscles, epithelial cells, and the remains of red blood corpuscles undergoing degenerative changes. The general appearance of the gland is shown in Fig. 1 and Fig. 2, which were taken from transverse sections

FIG. 2.



Transverse section of one lobe of thyroid gland of monkey, showing one portion of parathyroid at right edge of section and another triangular portion embedded in and just below centre of thyroid gland.

through the lateral lobe of the thyroid gland of a bonnet monkey. These and the other micro-photographs which will be shown later have been kindly prepared from my specimens by Dr. R. A. Bolam. These illustrations also show how closely in this animal the parathyroid is attached to the thyroid gland in which it may be even partly embedded, as in Fig. 2, an association to which I shall refer more fully in dealing with the functions of the gland.

Formation and Absorption of Thyroid Secretion.

The colloid substance is the secretion of the epithelial cells which line the alveoli. Hürthle has shown by observations made on normal glands and on portions of glands in which increased secretory activity had been stimulated either by removal of the greater part of the gland or by ligature of the bile-duct so as to cause absorption of bile-products into the blood that the secretion may be formed by the epithelial cells in two ways. The colloid may be either formed in droplets in the cells and then gradually extruded into the lumen of the alveolus or whole cells may break down and be discharged into the colloid substance, a part of which they thus help to form. In the first method the same cell continues to secrete, while in the second its place is taken by one of the reserve cells. It is doubtful if both these methods obtain during normal secretion, the first being probably the usual manner in which secretion takes place. The large amount of secretion which is found in many alveoli indicates that under ordinary circumstances it is not discharged as soon as it is formed, but that the central portion of the alveolus serves as a reservoir where the secretion is stored for a time before it finally escapes from the gland.

As the thyroid is a ductless gland it is clear that the secretion can only escape by the lymphatics or the veins. The evidence which we possess shows that the former is the usual path, for it was shown by King and by Horsley [8] that by applying pressure to the gland the colloid could be squeezed from the acini into the interacinous lymphatic spaces where it could be seen with the microscope. Biondi and Hürthle have found that this escape of the secretion from the alveolus may occur in two ways. The walls of the alveolus, not necessarily as the result of distension, becomes thinned out at one point and finally ruptures, allowing the colloid to escape directly into the lymphatic space outside while the empty follicle collapses and forms the starting-point for a new one. Hürthle has found that the secretion can also pass out from the alveolus without rupture of the wall. He injected Berlin blue into the lymphatic spaces of the gland, using an intermittent pressure, and found that it passed on into the interior of the alveoli through minute intercellular channels in which it could be seen. He also found that when the secretory activity was stimulated the colloid itself could be seen lying in these intercellular channels continuous with the colloid in the alveolus at one end and with that filling the lymph spaces at the other, proving that it was passing from the former position to the latter. By one or other of these methods, then, the secretion flows into and mingles with the lymph which bathes the interalveolar spaces of the gland and with it flows along the path already described to be discharged into

[8] Brit. Med. Jour., Feb. 6th, 1892.

the blood-stream in the innominate vein and so distributed to all parts of the body. No doubt as in other glands the activity of the secretion varies according to circumstances; of these, however, we possess but little information. Stimulation of the laryngeal nerves or of the sympathetic with the faradaic current produces no change indicative of increased secretion. Pilocarpin produces a marked increase in the secretion of the colloid as shown by Wyss, and Schäfer found that the changes produced in the cells were similar to those which occur in other secretory glands under the stimulating influence of this drug. As already mentioned the presence of an excess of bile constituents in the blood after ligature of the bile duct also stimulates thyroidal secretion. Removal of the greater part of the gland was also shown by Hürthle to serve as a stimulus to more active secretion in the remaining portion.

Composition of Thyroidal Secretion.

At one time the thyroid gland was considered to be an excretory rather than a secretory gland and the excretion a mucinoid substance the retention of which led to an accumulation of mucin in the body and the production of the subcutaneous swelling in myxœdema. Further investigation has shown that the colloid substance is a true secretion which does not contain mucin. Our knowledge of the actual composition of this secretion is by no means complete but several important constituents have now been separated from it. Most of those who have examined the composition of the secretion have considered the proteids to be the important and active constituent of it. Notkin [9] regards thyreoproteid, a substance which he isolated from the gland, as an active constituent which behaves like an enzyme. Gourlay [10] found that a nucleo-proteid was the only proteid to be obtained from the thyroid in any quantity and that it contained phosphorus which by Morkutun's analysis has been shown to amount to 0·32 per cent. Baumann and Roos [11] made the important discovery that the colloid substance contains iodine in an organic combination with proteid which they named "thyroiodin." This substance contains 9·3 per cent. of iodine and 0·56 per cent. of phosphorus. Hutchison [12] has found that two proteids are contained in the gland, a nucleo-albumin which is contained in the epithelial cells and a colloid material which fills the acini. The formed secretion of the gland is split up by gastric digestion into two parts, one of which is proteid, contains only a small amount of iodine, and has but slight physiological action, the other of which is non-proteid, contains more iodine and all the phosphorus of

[9] Semaine Médicale, April 3rd, 1895.
[10] Journal of Physiology, vol. xvi., 1894, p. 23.
[11] Zeitschrift für Physiologische Chemie, Band xxi., 1896, p. 481.
[12] Journal of Physiology, vol. xx., 1896, p. 474.

the original colloid, and is more active in removing symptoms due to loss of thyroid secretion than the proteid portion. S. Fraenkel[13] obtained a crystalline substance with the formula $C_6H_{11}N_3O_5$ from the gland which he named "thyreo-antitoxin"; there is, however, no satisfactory evidence to show that this body is endowed with active properties.

It is evident from these observations that the secretion is a complex body and we cannot as yet say whether its remarkable properties depend on one or, as is more probable, several constituents. Be this as it may we shall now consider what functions are fulfilled by the secretion as a whole, for that is the form in which it mingles with the blood and is thereby conveyed to the tissues.

The Results of Loss of the Secretion in Animals.

A large amount of valuable information as to the properties and functions of this secretion has been obtained by observing what occurs when it is no longer present in the blood. This state of affairs is easily brought about by removal of the gland from an animal. Owing to the superficial position of the gland in the neck this operation can easily be performed so as to entail no other secondary result than the loss of thyroid secretion forthwith, provided only that the parathyroid glands are not attached to the gland and removed with it, in which event the effects observed are the results of thyroidectomy plus parathyroidectomy. In man the results of failure of the normal supply of thyroid secretion from disease of the gland are seen in primary myxœdema and from removal of the gland for goitre in secondary myxœdema or "cachexia strumipriva" as it is also called. My own observations of the results of thyroidectomy have been made on rabbits and monkeys. It has, however, been shown that although no effects have been observed in fishes, in lizards and snakes the operation is followed by loss of strength and activity, ending in death in the course of a few weeks. In rabbits the different results obtained by various observers were difficult to explain until it was shown by Gley[14] that removal of the parathyroid glands along with the thyroid gland produced different effects from the removal of the thyroid alone. The double operation was followed by acute symptoms, the most important of which were muscular tremors commencing in the masseter muscles, clonic and often tetanic contractions of the voluntary muscles, paralysis of the extensors of the fore feet followed by that of the hind limbs, difficult and often rapid respiration, salivation, dilation of the pupils, and rise in temperature. Removal of the thyroid gland alone was followed by no such immediate effects.

[13] Wiener Medicinische Blätter, 1895, 48.
[14] Archives de Physiologie, 1892.

My own observations show that although the immediate effects of thyroidectomy are very slight, after a long interval a chronic cachexia develops closely resembling myxœdema in man. Thus in two rabbits which were kept for a long time under observation after the thyroid gland had been removed there was an early development of hebetude and loss of appetite; no further change was noticed until an interval of 11 months in one case and 12 months in the other had elapsed after the operation. After this, in addition to the hebetude already mentioned, swelling of the subcutaneous tissues, dryness of the skin, loss of hair, and subnormal temperature developed—an entirely different condition from that described by Gley after removal of the parathyroids as well. The illustrations show the appearance of one of these animals killed 11 months after the operation and the ears of the other killed 21 months after. The ears were very dry, rough, and cold to the touch though they flushed readily when handled. The edges of the ears were dry and cracked to a depth of a quarter of an inch. In many places this dried margin had broken off, leaving an irregular outline to the ear. In a third rabbit which was kept for 27 months after thyroidectomy no symptoms appeared. When the animal was killed the reason of this was found to be that some of the glandular tissue had unintentionally been left at the time of the operation and had undergone compensatory hypertrophy. The total amount of thyroid tissue found weighed only 0·07 gramme or about one-third of the weight of the gland of a normal rabbit, but it had been sufficient to maintain an adequate supply of secretion for more than two years. Dogs and cats both develop a rapidly fatal cachexia after thyroidectomy. More than 40 years ago Schiff showed that dogs did not long survive the operation and in 1884 he found that 59 out of 60 dogs rapidly succumbed after total extirpation of the gland. In dogs the total duration of the symptoms induced by the operation may vary from a few days to five weeks, but it rarely exceeds this period. Soon after the operation the animal becomes dull and listless and loses its appetite. These symptoms are followed by fibrillary twitchings in the muscles and clonic convulsions of the trunk and limbs, during which the animal lies on its side with the head thrown back and the limbs extended. There is great dyspnœa during these attacks and the animal is in a half comatose condition which becomes complete before death. There is a general diminution of muscular power and in many cases rapid emaciation. There is a slight rise of the temperature at first which becomes sub-normal before death. The red corpuscles are diminished and the white are increased in number. Very similar symptoms occur in cats. The observations of Vessale and Generali [15] on cats and dogs, of

[15] Rivista di Pathologia Nervosa e Mentale, vol. i., 1896.

Edmunds[16] on dogs, and of Welsh[17] on cats show that if the parathyroid glands are excised without the thyroid gland very similar acute symptoms occur to those observed when the thyroid and parathyroids are removed together. These symptoms are tremors, slow and unstable gait, emaciation, and weakness, all of which previously were regarded as being due to the loss of the thyroid alone. The most important results of all have been obtained in monkeys which have been employed by Munk, Horsley,[18] and myself. In the bonnet monkey (macacus sinicus) which I have used with one exception in all my experiments[19] a parathyroid gland lies in close connexion with or actually embedded in each lobe of the thyroid gland, as is shown in Fig. 1 and Fig. 2. As a result of this when the thyroid gland is removed the parathyroids are removed along with it. It would be difficult to remove the one without the other, for distinctly as the parathyroid can be seen in a transverse section it is much more difficult to see it during life while the gland is *in situ*. In two recent experiments I was unable to detect even with a lens the parathyroids on either side and to remove them without the thyroid gland; they were, however, easily seen in transverse sections of the lateral lobes after removal of the whole gland. It is therefore important to bear in mind that thyroidectomy in this monkey involves removal of the parathyroids as well, so that the symptoms which occur afterwards are not solely due to loss of thyroid secretion but in part are due to loss of the parathyroids as well.

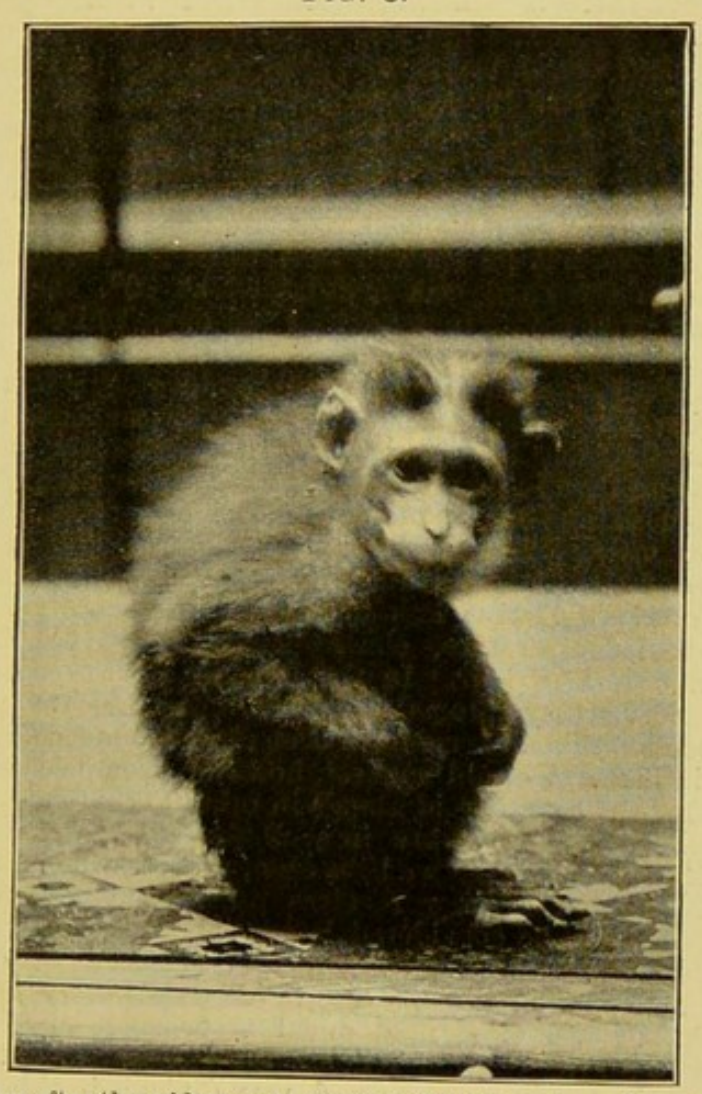
I have removed the whole or a part of the thyroid gland in nine bonnet monkeys and in one rhesus monkey; in four of the former the symptoms were allowed to develop with the object of testing the influence of various preparations of the thyroid gland upon them. Some symptoms also occurred in the others, but these four form the basis for the description of the symptoms which result from the operation. These symptoms have been very carefully described by Horsley, but they have such an important bearing upon the whole subject that I shall briefly describe what I was able to observe in my own experiments. The gland is readily removed in the following manner when the animal is fully under the influence of ether. The skin of the front of the neck is shaved and carefully washed with one in 1000 solution of perchloride of mercury. A median longitudinal incision is made through the skin overlying the thyroid and cricoid cartilages and upper part of the trachea. On separating the muscles and exposing the upper part of the trachea the isthmus comes into view. Each lobe is then gently separated from the surrounding structures

[16] Journal of Pathology, vol. iii., 1896.
[17] Ibid., vol. v., 1898.
[18] Report of the Clinical Society on Myxœdema, 1888.
[19] The expenses have been partly defrayed by a grant from the Scientific Grants Committee of the British Medical Association.

and while the gland is held by one pair of forceps the blood-vessels are torn out of it at the point of entrance by another pair. The loss of blood is trifling and no ligatures are required. The usual antiseptic methods are adopted and the muscles are united by a couple of sutures. The skin is brought together with horsehair sutures set very close. The wound is dressed with carbolic gauze or some antiseptic wool and collodion and it heals rapidly by first intention. After the operation the animals have been kept in a room the temperature of which ranged between 60° and 70° F. In about five days the symptoms first begin to develop, the early symptoms being entirely nervous. One of the first to appear is a fine regular tremor which is most easily seen in the upper limbs but which is also plainly visible in the lower limbs as well when the animal is held with the feet unsupported. Along with the tremor there is a marked change in the whole demeanour which is the more noticeable owing to the naturally lively disposition and active habits of the healthy monkey. There is progressive apathy with loss of natural curiosity and interest in surrounding objects, while the temper is irritable, interference being resented. There is loss of activity, as the animal sits still in one place on a perch or on the floor of the cage for long periods without moving; and there is increasing loss of muscular power, as climbing is done more slowly and evidently with greater effort as the symptoms advance. The attitude assumed is characteristic: the head is bent, the trunk is curved forwards, and the knees are drawn up so that the chin rests upon them, the joints of all four limbs being in a position of flexion. This attitude is well shown in Fig. 3 taken from one of my animals. Contractures owing to tonic spasm of the flexor muscles frequently occur; in fact, this attitude is, I believe, partly a result of these contractures as the limbs are often found to be rigid when it is adopted. Clonic contractions of the muscles are common. There may be a single contraction of a group of flexor muscles or a series of three or four may involve all the flexors of one arm, increasing in intensity until a position of extreme flexion at all the joints is reached, after which relaxation takes place until another series occurs. Irregular fibrillary contractions of the superficial muscles are often visible through the skin. In consequence of these symptoms the gait is stiff and unsteady, and when the contracture is excessive the animal is obliged to walk on the heels owing to the tonic spasm of the flexors of the ankle raising the toes and sole of the foot from the ground. There is a marked tendency to fall over backwards, so that if a banana is held over the animal's head it loses its balance in looking upwards at it and falls over backwards and a very slight push when the animal is sitting has a similar effect. True epileptic fits of greater or less intensity may occur. There may be a sudden loss of consciousness, so that if the monkey is on the perch at the time it falls to the ground. In one case I observed several epileptic fits in succession in

which there was loss of consciousness, tonic spasm of the flexor muscles of the limbs, with risus sardonicus, followed by clonic contractions and micturition. In one fit there were in addition double internal strabismus with retraction of the eyelids and conjugate deviation to the left. Retraction of the head and salivation were also observed. I have seen a temporary inability to use the arms owing to spastic

FIG. 3.



Monkey after thyroidectomy, showing attitude and swelling of face.

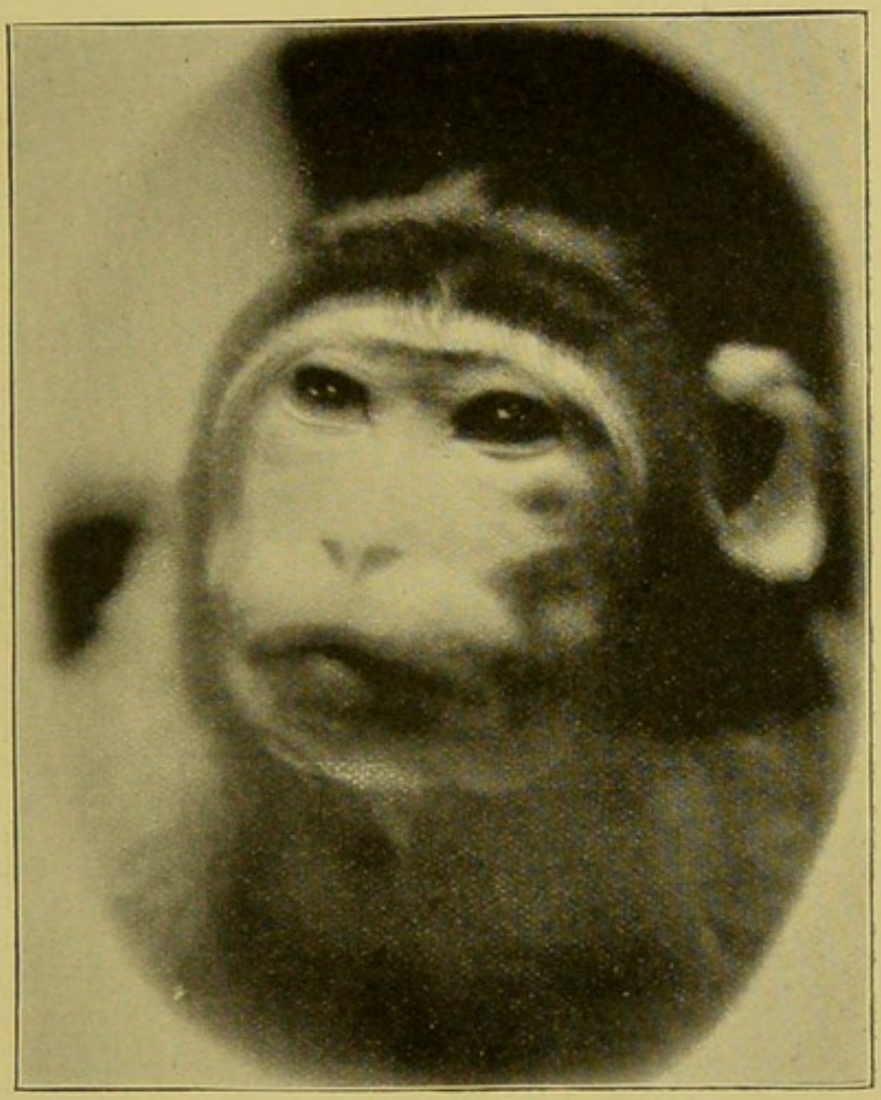
rigidity limiting the movement, but not actual paralysis as described by Horsley who twice observed a complete temporary hemiplegia. The temperature at first is raised and irregular, but it soon becomes subnormal. Thus in one experiment the rectal temperature, which is usually 100° F. in this monkey, was only twice below normal during the first week following the operation, as it otherwise ranged between 100° and 102°. During

the second week it only once rose to the normal level, being otherwise between 98° and 99·6°, while in the third week it varied between 97·6° and 100°, except on two evenings when it rose to 101° and 102·4°. In one experiment I found the temperature as low as 80° four days before death.

During the second and third weeks the myxœdematous swelling becomes distinct and, as in man, is most apparent in the face. Both upper and lower eyelids become swollen, and with this there is sometimes transverse wrinkling of the forehead. Both lips are also swollen by the elastic œdema. The appearance of the face is shown clearly in Fig. 3 and Fig. 4 which were taken from two different monkeys. The skin, more especially of the ears, becomes dry and rough, and the hair may be shed. Examination of the blood shows that the red corpuscles are diminished and the white increased in number. The average duration of life was found by Horsley to be 24 days, but he showed that when the temperature of the air in the cage was maintained at 90°, the average duration of life was increased to 125 days while the symptoms ran a more chronic course, like those of cretinism in man. Without giving any further details of this interesting condition its resemblance to primary myxœdema in man is remarkable. The course of the symptoms is much more acute than in man, partly because the supply of thyroid secretion is cut off suddenly by the operation, while in primary myxœdema the supply only gradually fails as the disease of the gland advances. In both conditions we have the same progressive loss of mental and bodily activity, subnormal temperature, elastic subcutaneous œdema, dry skin, and loss of hair. In the monkey we have, however, acute nervous symptoms which do not occur in primary myxœdema, though some have been observed after thyroidectomy in man. I would suggest, however, from the results of removing the parathyroid glands in rabbits and other animals that these symptoms are in part due to the loss of the parathyroids which, as we have seen, are removed along with the thyroid. This view receives further support from the fact which will be considered later, that these acute nervous symptoms are not readily controlled by treatment with thyroid extract as might be expected were they purely thyroidal in origin. The close anatomical association of the parathyroid with the thyroid renders the removal of the former without the latter, or *vice versâ*, very difficult in this animal. Under these circumstances we can remove both together and afterwards give thyroid extract to prevent the onset of symptoms from loss of thyroid secretion. The symptoms which then occur, as I hope to show in my next lecture, are nervous in origin and are due, I believe, to the loss of the parathyroids. Opportunities of observing the effects of total thyroidectomy in man have occurred in cases in which that operation has been performed for goitre. It is well known that in a certain number of these cases as a result of the loss of the thyroidal secretion symptoms develop which are identical with those

of primary myxœdema. Indeed, it was the striking similarity between the two noticed by Sir F. Semon which led to the appointment of the committee by the Clinical Society of London, whose report proved the identity of the two conditions and their dependence upon loss of function of the thyroid gland.

FIG. 4.

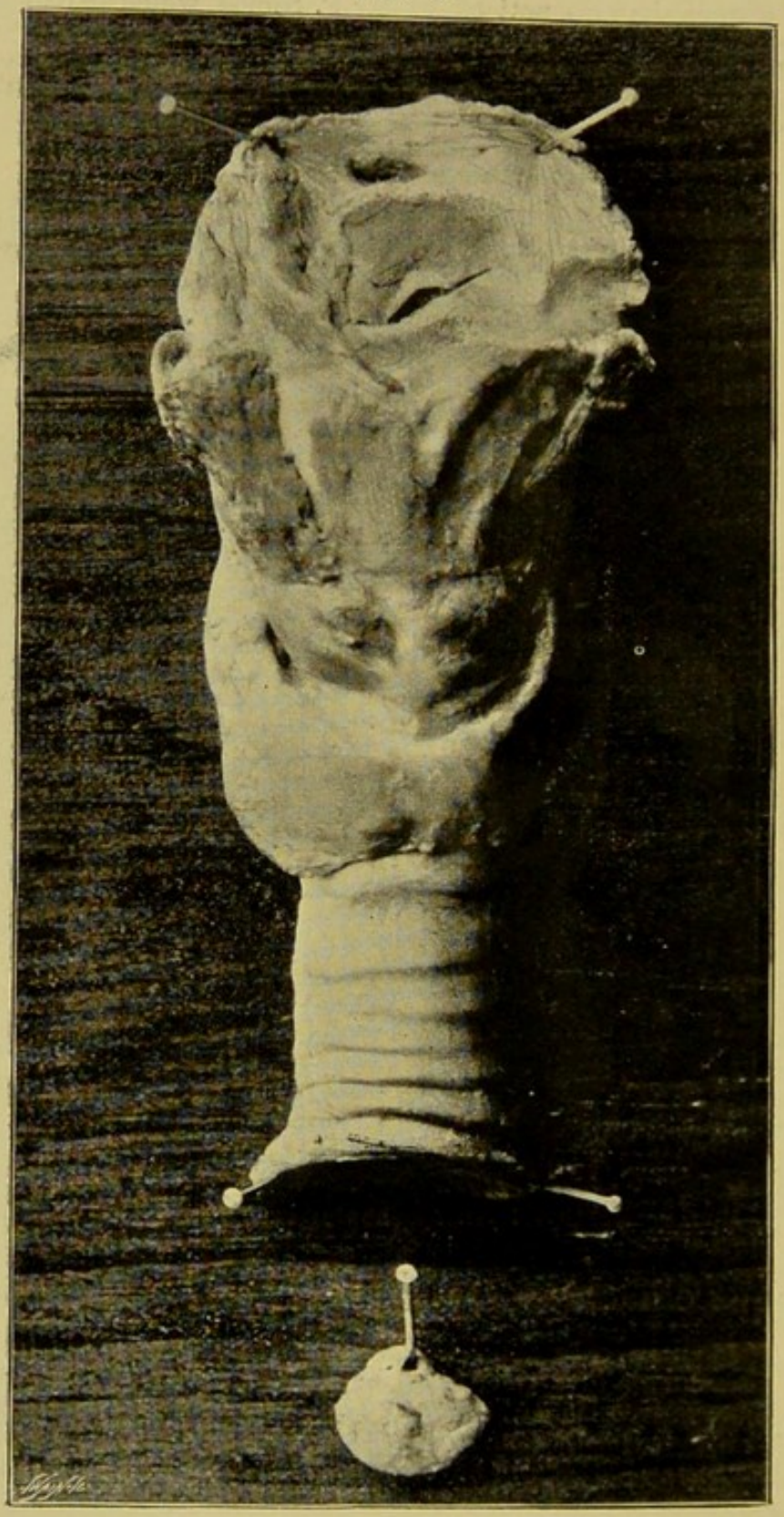


Monkey after thyroidectomy, showing swelling of eyelids and lips.

THE CHANGES IN THE GLAND IN PRIMARY MYXŒDEMA.

In man only three of the diseases which occur in the thyroid gland appear to be capable of causing a sufficiently destructive lesion of the secretory cells to materially diminish the amount of secretion. Syphilis and actinomycosis of the gland have thus caused myxœdema. If these diseases are successfully treated the gland recovers, sufficient secretion is once more formed, and the myxœdema

FIG. 5.



Thyroid gland and pituitary gland from a case of myxœdema.

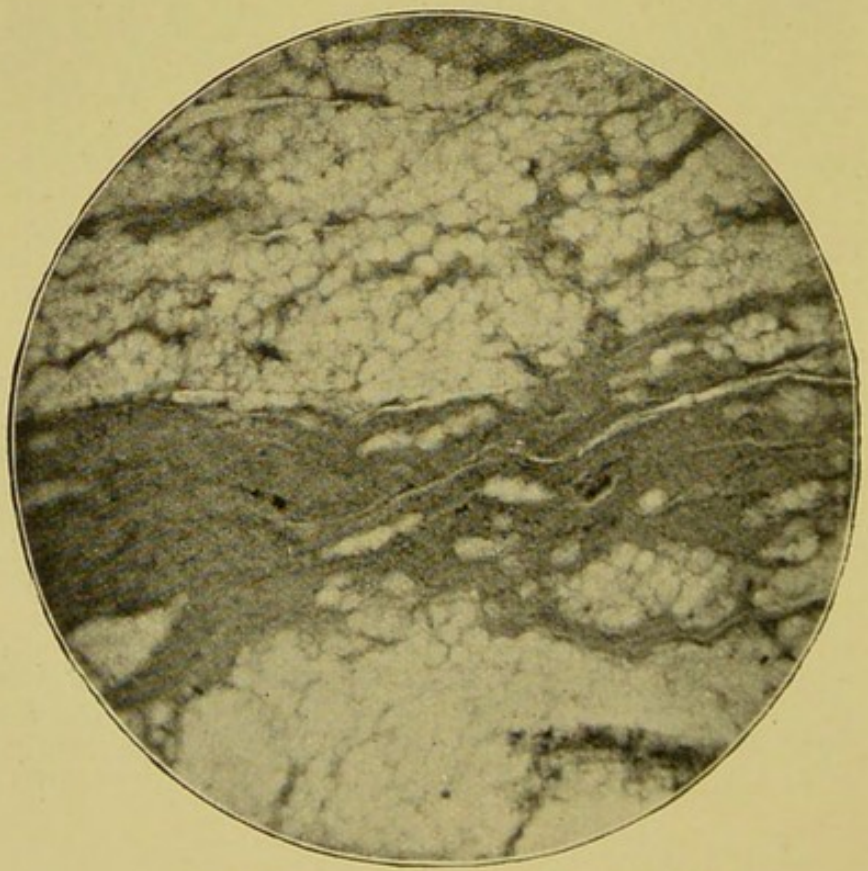
disappears. The great majority of cases of primary myxœdema are due to a fibrosis of the gland with atrophy of the secreting epithelium. Unfortunately, we know very little as yet of the cause or mode of origin of thyroidal fibrosis. It may, according to the older views, be regarded as a chronic inflammation, a chronic interstitial thyroiditis, as a result of which new fibrous tissue is formed which by its slow contraction and constriction of the blood-vessels and alveoli leads to the destruction of the epithelial cells. On the other hand, it seems more probable that the atrophy of the glandular tissue takes place primarily as the result of the action of some toxic agent and that the fibrosis is only a replacement fibrosis such as occurs in the spinal cord and elsewhere after more highly organised structures have been destroyed. This problem, which is one with that of the origin of fibrosis of other glandular organs such as the liver and kidney, does not concern us further here, for however it originates the result of the disease is a slowly progressing destruction of the gland with gradual diminution and final arrest of secretion.

The structural changes in thyroidal fibrosis may be very extensive—thus in one specimen, for which I am indebted to Dr. Callcott of Gosforth, the whole gland was much diminished in size and pale-yellow in colour. The right lobe measured one and a quarter inches in length and the left lobe one and a quarter inches, and the isthmus a quarter of an inch in width. The general appearance is shown in Fig. 5. The day after it had been removed and placed in spirit it weighed 3·52 grammes, or only about one-tenth of the normal weight. The microscopical structure is shown in Fig. 6, from which it will be seen that only a few scattered alveoli are left and even in some of these only a few of the epithelial cells still survive. The rest of the gland is made up of richly nucleated areas of young fibrous tissue divided by wide strands of older fibrous tissue with few nuclei. In another case in which death occurred from mitral disease 18 years after the onset of the myxœdema, for the last six of which she had been treated by thyroid extract, the gland was pale-yellow in colour and weighed 4·5 grammes. The whole of the gland, as is shown in Fig. 7, was converted into fat and fibrous tissue and not a trace of the original glandular structure remained. It is therefore quite evident that very little if any secretion would be formed in the gland shown in Fig. 6 and certainly none at all in that shown in Fig. 7, in which for long there must have been complete arrest of thyroidal secretion. The symptoms of myxœdema which occur in man as a result of this destructive disease of the gland were so ably described by Dr. Ord in his Bradshaw lecture last year that they are familiar to all. I should, however, like again to draw attention to the fact that there are many cases of early thyroidal fibrosis in which the symptoms are not nearly so definite as in the advanced cases. I have endeavoured in

FIG. 6.

Thyroidal fibrosis with advanced atrophy.

FIG. 7.



Thyroidal fibrosis with complete atrophy.

a recent paper to show what are the chief characteristics of these cases, such as slight subcutaneous swelling and dryness of the skin, normal temperature, certain striking subjective nervous symptoms, &c. The opportunity of examining the condition of the gland at this early stage can only arise if death should occur from some accident or intercurrent disease. In the absence of definite information we can only conjecture that a much earlier stage of fibrosis will be found, for it is evident that in any given case the severity of the symptoms will vary directly with the amount of atrophy of the glandular structure. The gradual changes in the appearance of a patient suffering from slowly progressing fibrosis of the thyroid gland will be illustrated by some photographs which will be shown at the next lecture, in which I shall deal with results of disease of the thyroid gland in the young and the rational treatment of myxœdema and cretinism.

LECTURE II.[1]

Results of Loss of Thyroid Secretion in the Young.

Mr. President and Gentlemen,—So far we have considered only the results of athyroidism in adult animals and man, but thyroid secretion plays such an important part in the metabolism of normal growth of the young that it is necessary to consider the results of its loss in young animals and children when in addition to other symptoms we find arrest of development. Hofmeister[2] found in young rabbits from five to 16 weeks old that thyroidectomy was followed by arrest of growth of the bones and especially of the long bones. The skin became rough, the hair was shed, and the abdomen swelled. Von Eiselsberg[3] removed the thyroid gland from two male lambs eight days old and kept a third similar lamb as a control. So marked was the arrest in growth that seven months later when the control lamb weighed 35 kilogrammes the two others only weighed 14 and 10 kilogrammes each. The two together thus weighed little more than two-thirds as much as the normal animal. The lesser lamb had a small head with rudimentary horns and subnormal temperature. These experiments show how essential a normal supply of thyroid secretion is to natural growth in young animals. Of special interest in this connexion is the remarkable case recorded by Bruns,[4] in which Sick removed an entire goitre from a boy 10 years of age. 18 years afterwards Bruns examined the patient and found that bodily development had been arrested from the time of the operation. The expression of the face was idiotic and there was well-marked swelling of the subcutaneous tissues, especially of the eyelids and lips. The skin was dry and the hair was scanty. The mental capacity was even less than that of an average boy of 10 years of age. The speech was slow and he could do no work. In short, the case was one of advanced secondary cretinism readily explained by the fact that neither before nor after death could any trace of thyroidal tissue be found.

[1] Delivered on March 9th, 1899.

[2] Fortschritte der Medicin, 1892.

[3] Verhandlungen der deutschen Gesellschaft für Chirurgie, XXII. Congress, 1893.

[4] Volkmann's Sammlung Klinischer Vorträge, No. 244, 1884.

When arrest of development or destructive disease of the thyroid occurs early in life we find that the symptoms of primary cretinism, which are the same in the sporadic as in the endemic form, soon begin to appear. I can best illustrate the characters of this remarkable condition by a short description of a case which I have had the opportunity of seeing several times during the last few years with Dr. Bunting of Scotswood. A single woman, aged 28 years, was first seen in June, 1895. In infancy the mother noticed that the extremities became blue and cold after washing and that the abdomen was prominent. After a fall in which the back was hurt at nine months of age growth became arrested and the symptoms of cretinism gradually developed. The patient now has the symptoms of advanced cretinism. She is only 34½ inches in height and the head looks relatively large, the forehead being broad and flat. The anterior fontanelle is not quite closed by bone, though it has a dense thick covering which yields but slightly when firm pressure is made. The hair is dark, fairly abundant, and coarse, but it grows well. The scalp is dry, rough, and scaly. The appearance of the face, body, and limbs shown in Fig. 12 is very characteristic. The expression is generally dull and fixed, but a broad grin appears at once if she is amused. The skin has a yellowish tint, but there is a slight flush in each cheek. All parts of the face are very considerably swollen, especially the eyelids, cheeks, and lips. The nose is short, broad, and turned up at the end. The mouth is large, the lips being thick and everted. The tongue is large and generally protrudes from the open mouth. The teeth are ill-developed and carious. The mother thinks that she has never yet lost her first set of teeth. The ears are large and prominent. The neck is short and thick and no trace of a thyroid gland can be felt. The subcutaneous swelling forms a soft elastic pad just above each clavicle. The abdomen is protuberant and there is a small umbilical hernia. The limbs are all short and stunted in appearance. There is well-marked lordosis of the spine. Both feet and hands are swollen and cold. The skin as a whole is dry and rough. There are two pigmented moles, one on the chest and the other on the cheek. The mammary glands are rudimentary, like those of a child, and there is no pubic hair. Menstruation has only occurred a few times and the flow has been very scanty. Her temperature is 96·3° F. at 3.30 P.M. She cannot read, write, or even dress herself. She can feed herself if inclined and sleeps well. She can walk slowly but rarely leaves the house and may be left alone in a chair without moving for two hours. The vocabulary is limited to a few words, such as "Ma," "Thomas," and "Pussy." She is easily amused and sometimes has fits of almost uncontrollable laughter. Such is the state which results from insufficiency, if not total suppression, of thyroidal secretion for 27 years. I shall refer to the subsequent histology of this case later.

As in myxœdema in the adult so in cretinism we find different degrees of severity. As the success of treatment depends so much upon an early start being made with it I would urge the importance of carefully considering the possibility of cretinism in all cases where some arrest of development is noticed early in life. We find various intermediate types between the extreme forms of which I have given an example and ordinary myxœdema dependent upon the age at which the disease first commenced. The older the child at the time of the onset the less marked the want of development and the more nearly the disease resembles the adult type.

Renewal of Thyroid Secretion.

(*a*) *By grafting.*—The various results of athyroidism which we have just considered show that a sufficient supply of thyroid secretion is essential for the completion of the chemical changes in the cell which constitute normal metabolism and which, as might be expected, are even more important during the period of growth than in the adult. When the supply of the secretion is renewed, by means we shall now consider, metabolism is once more completed in a normal manner, the central nervous system and other tissues return to their natural condition, and in cretins the metabolism is so markedly re-awakened that general growth which may have been arrested for 10 or even 20 years again progresses, sometimes with surprising rapidity. The maintenance of a supply of thyroid secretion by artificial means when the natural source has failed is thus a question of great practical importance. The experiments of Schiff and von Eiselsberg[5] showed that a portion of a thyroid gland which had been successfully transplanted into the subcutaneous tissues of a dog or cat was able to maintain a sufficient supply of secretion after removal of the animal's own gland from the neck to avert the acute symptoms of athyroidism which usually follow this operation. A great advance was made by Victor Horsley[6] who suggested that a similar procedure should be adopted in man to arrest the inevitable progress of myxœdema to a fatal termination. This method of treatment was carried out with good results by Bircher[7] and by Bettencourt and Serrano[8] as a marked improvement in the symptoms followed the operation. Unfortunately, the grafted gland does not appear to be able to maintain its independent existence for long, as after a time its function ceases and the symptoms return. In only one case has the improvement been manifested for more than a few months. This was

[5] Ueber Tetanie in Anschlusse an Kropf-Operationen, 1890.
[6] Brit. Med. Jour., Feb. 8th, 1890, p. 287.
[7] Sammlung Klinischer Vorträge, No. 357.
[8] La Semaine Médicale, August 13th, 1890.

in a case of myxœdema with melancholia recorded by MacPherson[9] in which all the symptoms disappeared after the operation and had not returned three years later.

(*b*) *By thyroid extract.*—The immediate improvement observed by Bettencourt and Serrano after grafting was attributed by them to absorption of the juice of the transplanted gland by the tissues of the patient. It then occurred to me that a much simpler method of maintaining the necessary supply of thyroid secretion would be the continued internal administration of the secretion itself. It has long been good practice to supply any deficiency in the secretion of the glands of the stomach by means of a glycerine extract of the peptic glands—an acid glycerine of pepsin. I therefore prepared a glycerine extract from the healthy thyroid gland of the sheep as a convenient form in which to give the secretion. There is no need for me to describe the actual method of preparation or composition of this thyroid extract as the original preparation has now been included in the New Pharmacopœia under the name of "liquor thyroidei." As the secretion normally passes into the blood mixed with the lymph I decided in testing the efficiency of the extract to inject it beneath the skin so that it might be absorbed by the lymphatics and so enter the blood as nearly as possible under normal conditions. This method was used at first both in man and in animals and by it the efficiency of the remedy was proved. It was afterwards shown independently by Howitz,[10] E. L. Fox,[11] and H. Mackenzie[12] that the extract was equally efficient when given by the mouth, so that this simpler method has since been employed both in animals and in man.

Thyroid Extract in Athyroidism in Animals.

The treatment of monkeys after thyroidectomy by thyroid extract has yielded some interesting results which help us to distinguish between the symptoms due to loss of the parathyroid from those due to loss of the thyroid when both these glands are removed at the same time. The following is a brief summary of the results I have obtained.

1. A male bonnet monkey. The thyroid gland was removed in the usual manner. No symptoms appeared during the first week after the operation. At the beginning of the second week there was a fine tremor of the arms and hands. Examination of the blood showed a slight diminution of the number of both red and white blood corpuscles. During this second week there was diminution

[9] Edinburgh Medical Journal, May, 1892.
[10] Ugeskrift for Laeger, Nos. 7, 8, 1892.
[11] Brit. Med. Jour., Oct. 29th, 1892, p. 941.
[12] Ibid., Oct. 29th, 1892, p. 940.

of activity, increase of the tremors, and there were occasional clonic contractions of the muscles of the arm and forearm. A slight swelling of the upper and lower eyelids appeared. In the fourth week there was marked inactivity, the characteristic attitude was adopted, and the tremors were well marked. There was distinct myxœdematous swelling of the eyelids and lips. The red corpuscles were diminished and the white increased in number. The temperature showed marked daily variations and was subnormal on three mornings. On the twenty-sixth day treatment was commenced by subcutaneous injection of thyroid extract and continued till the forty-fourth day, 20 minims in all being injected during this period. As a result of this treatment during the fifth week the tremors, swelling, and anæmia all diminished and there was more activity. The morning temperature still continued to fall and was only 95·4° on the twenty-second day. The following day the animal had an epileptic fit followed by an increase of the tremors and fibrillary muscular contractions and spastic rigidity of the flexors of the limbs lasting for some hours. After this the improvement steadily continued till at the end of the seventh week all the symptoms had disappeared and with the exception of a slight loss of weight the monkey was as well as before the operation. The treatment was discontinued and the symptoms returned again much in the same manner as they had at first. Treatment was again resumed but too late, as dysentery developed in addition to the myxœdematous symptoms and the animal died 13 weeks after the operation. Fig. 3 shows this animal after the return of the symptoms.

II. A male bonnet monkey. In this case the symptoms first began two days after thyroidectomy and were well marked by the fourteenth day when treatment was commenced by injections of a solution of the alcoholic precipitate of thyroid extract in glycerine and water. The symptoms had disappeared by the twenty-sixth day. The symptoms again returned and although improvement followed the use of thyroid extract death occurred after several severe convulsions on the sixty-ninth day.

III. In this experiment the symptoms commenced as early as the first day after thyroidectomy. Treatment was commenced on the fifth day by injections of a solution of a nucleo-albumin prepared from fresh thyroid glands by Halliburton's method in a 2 per cent. solution of sodium carbonate. There was some temporary improvement in the symptoms, but they returned in spite of continued treatment, and death took place on the twelfth day. This experiment, however, is of doubtful value, as Hutchison[13] has since maintained that a solution thus prepared would not contain the active secretion of the gland.

[13] Journal of Physiology, vol. xx., 1896.

In these three experiments, though the actual presence of the parathyroid glands in the thyroid was not proved by microscopical examination, there can be little doubt that they were removed with it. In the two following experiments the animals were treated with thyroid extract for some time before as well as after the removal of the thyroid gland along with the parathyroids as ascertained by microscopical examination.

IV. A small male bonnet monkey was given one minim of thyroid extract by the mouth per diem for 44 days and then three minims daily for the next 31 days when the thyroid and the parathyroid glands were removed. The same dose of three minims was continued after the operation. No symptoms at all developed till the forty-second day after the operation. On this day it was noticed that on climbing down from the perch the monkey fell part of the way on to the floor of the cage and was unable to climb up again. It then showed general fibrillary twitching of the muscles in all parts of the body. The arms were rigid owing to spasm of the flexor muscles, which could be overcome without much difficulty but returned at once. The legs also were flexed at all the joints except the ankle-joints, which were extended. There was no subcutaneous swelling of the face or elsewhere. The rectal temperature was 100·6° F. A dose of six minims of liquor thyroidei was given but the animal became worse and died the same day.

V. A small male bonnet monkey was given one minim of thyroid extract by the mouth for 44 days, the daily dose was then increased to three minims for the next 42 days, when the thyroid gland was removed with the parathyroid glands. The dose of thyroid extract was continued as before. On the eleventh day after the operation there was some loss of activity and the lower eyelids were slightly swollen. After this there was progressive loss of strength and activity and the eyelids and lips became more swollen. Spastic rigidity of the limbs developed and on the nineteenth day after the operation the animal was found lying dead at the bottom of the cage. The swelling of the face was largely due to the presence of a fluid œdema which escaped when the skin was incised.

It is thus evident that although in some cases the symptoms which follow thyroidectomy in monkeys disappear when the loss is made good by giving thyroid extract, in others there is only an improvement and death afterwards results with acute nervous symptoms. Edmunds[14] has also found that under similar circumstances thyroid extract produces a marked benefit but does not save the life of the animal. From these facts and from the results of removal of the parathyroid glands in other animals it

[14] Proceedings of the Royal Society, vol. lxiv.

seems most probable that the acute nervous symptoms in the monkey such as the fibrillary twitchings, the spastic rigidity, and perhaps also the tremor and convulsions are largely due to loss of the parathyroids, while the subcutaneous swelling, dryness of skin, loss of hair, subnormal temperature, and changes in the blood are due to loss of the thyroid secretion. This conclusion receives further support from the close resemblance of the latter symptoms to those of primary myxœdema in man which we know to be the result of disease of the thyroid glands, there being no evidence as yet to show that the parathyroids are affected in this disease. If this be the correct explanation it is not surprising that these particular symptoms are not influenced by the thyroid extract.

Treatment of Myxœdema by Thyroid Extract.

In primary and secondary myxœdema in man we see the results of loss of thyroid secretion pure and simple and consequently are able to remove the symptoms entirely by giving a sufficient supply of the secretion. Soon after I first determined to try this method of treatment in myxœdema I was fortunate enough to come across a well-marked case in a woman who, after the nature and experimental character of the treatment had been explained to her, was bold enough to give full permission for it to be carried out whatever the result might be. The patient having been shown at a meeting of the Northumberland and Durham Medical Society and the proposed treatment described it was commenced in April, 1891. The symptoms soon disappeared, proving the correctness of the conclusions which had led to the suggestion of the remedy. Nearly eight years have elapsed and this first case still remains free from myxœdema.

We may now briefly consider the method of carrying out this treatment of myxœdema. The main objects of the treatment are to remove the symptoms by restoring normal metabolism as rapidly as possible without risk to the patient, and when this has been accomplished so to regulate the treatment as to continue the supply of thyroid secretion in sufficient quantity to maintain the normal rate of metabolism of the tissues generally. For this purpose the treatment is divided into two stages. During the first stage the tissues are gradually brought back to a normal condition. This may, according to the severity of the symptoms, require from one to three months. As soon as the symptoms have entirely disappeared the first stage is completed. The condition of the atrophied thyroid gland is not influenced by the treatment so that if the artificial supply of secretion is discontinued at this or any other time of the patient's life all the symptoms of myxœdema will gradually return as I have found by actual experience. Thus the second stage of the

treatment of necessity lasts as long as the patient lives. It is therefore necessary to make the permanent daily dose as nearly as possible equivalent to the normal amount of secretion. If the dose falls below this slight symptoms of myxœdema will reappear and if it is excessive a condition of thyroidism will be produced.

Preparations of Thyroid Secretion.

Thyroid secretion can be given in several different forms. The actual gland itself containing the secretion may be used and is a useful form when the patient lives in some remote place or when it is necessary to make the treatment as inexpensive as possible. Arrangements can easily be made for the regular supply of one lobe of the thyroid gland of a freshly killed sheep twice a week by a butcher who has once been shown where the gland lies and the ease with which it may be removed. From one-eighth to one-quarter of a lobe is a suitable daily dose of the sheep's gland, one-quarter of a lobe being equivalent to about 10 minims of liquor thyroidei. As the raw gland is somewhat nauseous it should be minced and taken in glycerine or some similar vehicle in order to make it palatable or it may be lightly cooked on the outside by frying or boiling before it is eaten. As a rule, it is much better to employ one of the preparations of the thyroid gland rather than what may be termed the crude drug itself. Of these two are now official, liquor thyroidei and thyroideum siccum, the former of which is simply the original liquid thyroid extract. The liquor thyroidei is the most convenient preparation for general use and in my experience the most efficient. It is prepared from a considerable number of glands at a time, so that the strength is uniform. In prescribing it should be ordered in the undiluted form and not more than a sufficient supply for a fortnight should be obtained at one time. The patient must be provided with a minim measure glass and measure out the dose of five or 10 minims as the case may be, adding a dessertspoonful of water at the time it is taken. This preparation is conveniently given in a single daily dose at bedtime. The dry thyroid of the Pharmacopœia may be given as a powder or made up into a pill or tablet. If the dried preparation becomes damp at all it is liable to decompose and become unfit for use.

Method of Treatment.

In advanced cases the first stage of the treatment must be carried out with great caution, especially if any symptoms of degeneration of the cardiac muscle, such as attacks of syncope, dyspnœa on exertion, feeble or irregular pulse, or weak heart sounds are present. Under these circumstances the patient should be confined to bed at first and only small

doses of from three to five minims of liquor thyroidei given each night. This dose if well borne may be gradually increased up to 10 minims. If not confined to bed these patients are apt to make use of their returning vigour too soon, before the heart has had time to recover and to adapt itself to the altered conditions brought about by the treatment. These advanced cases in which little exercise has been taken for months or even years are now rare, but in the early days of the treatment the importance of this caution was painfully impressed upon me by the deaths of two patients from syncope who had cardiac disease, after they had practically got rid of the symptoms of myxœdema. Any undue acceleration of the pulse up to 90 or 100 indicates that a reduction should be made in the dose and any signs of cardiac failure must be met by giving stimulants and digitalis. By far the greater number of cases which require treatment are now seen in the early stages of the disease before any cardiac symptoms have developed. In these the patient is able to go about as usual, though it is advisable to avoid any unusual exertion during the first stage of the treatment. A daily dose of 10 minims of thyroid extract may be given each night from the beginning and increased to 15 minims at the end of a fortnight if decided improvement has not already taken place. Any marked increase in the frequency of the pulse or rapid loss of weight is an indication for at once reducing the dose. Symptoms of gastro-intestinal catarrh have sometimes arisen during this first stage of the treatment especially if the raw gland has been used. They rarely if ever appear if a suitable preparation of the gland is used instead. If they do occur the thyroid treatment should be stopped until they have passed away and then smaller doses should be given when the treatment is again commenced. In many cases no other treatment beyond the daily dose of thyroid extract is required. When, however, there is a well-marked anæmia it is a good plan to give iron as well as thyroid extract. Five grains of dried sulphate of iron in a pill twice or thrice daily after meals is a suitable form in which to give it.

As soon as all the symptoms of myxœdema have disappeared the first stage of the treatment is completed. The second stage then commences and must of necessity last as long as the patient lives. During this stage the patient must continue steadily to take a daily dose of thyroid extract equivalent to the daily output of the gland before it became diseased or at any rate of that part of it which has become functionless. It is important that patients should understand this and that good health can only be maintained by the continued use of the remedy. To ensure this it is often better to describe the remedy as an essential part of the daily diet and not as a medicine so as to overcome the objection some persons have to taking what they regard as a medicine for such long periods. Of course, an occasional intermission of the treatment for a

week or so has little or no effect, but if no thyroid extract is taken for three or four weeks the temperature falls one or two degrees below normal and the myxœdematous swelling of the face begins to develop again. If the extract is omitted for a longer period still all the original symptoms gradually reappear till at the end of three or four months the condition will be much the same as it was before any treatment was adopted. The most suitable dose for the second stage of the treatment is, generally speaking, 10 minims of the extract given once a day. If after a time any slight symptoms of myxœdema reappear the permanent dose should be increased to 12 or 15 minims. In none of my own cases has it been necessary to give more than 10 minims; in a few cases this dose is too large, as after a time it produces acceleration of the pulse. The permanent dose has then to be fixed at five or seven minims a day. In doubtful cases of myxœdema thyroid extract may be given as a means of diagnosis. For this purpose a dose of 10 minims should be given daily for three or four weeks. If the symptoms steadily diminish they are the result of thyroidal disease; if, on the other hand, no improvement takes place they are due to some other cause. This test is of great use in distinguishing some of the cases with anæmia and subcutaneous swelling from cases of anæmia with ordinary obesity which they often closely resemble.

Results of the Treatment of Myxœdema.

When the treatment of a well-marked case of myxœdema is carried out on the lines just indicated very definite and interesting results are soon obtained. One of the earliest signs of improvement is in the return of the temperature to the normal level. This is illustrated by one case in which the temperature before treatment ranged from 95° to 96° F., whereas during the second, third, and fourth weeks of treatment it varied between 96° and 98°. As the temperature rises to normal the former sensitiveness to cold is lost and the frequency of the pulse is increased. The most striking changes are those which take place in the skin with its appendages and in the subcutaneous tissues. The myxœdematous swelling gradually disappears from all parts of the body so that the face and hands once more assume their natural appearance and the free movement of the limbs which has been considerably hampered by the swelling is regained. The reduction of the swelling is accompanied by a loss of weight which may amount to as much as two or even four stones. The skin, which as a result of the removal of the swelling may for a time remain loose and wrinkled, becomes warm and moist owing to a renewal of the secretory activity of the sebaceous and sweat glands. Not infrequently there is some desquamation which may occur in fine scales or in

large flakes from the palms of the hands and soles of the feet, as observed by Byrom Bramwell.[15] The hair follicles resume their proper function, so that even where there has been complete baldness a good growth of hair is developed in the course of six or 12 months. Considerable changes are thus produced in the appearance of the patient and they are well illustrated by the four photographs shown in Figs. 8, 9, 10, and 11. They both illustrate the changes which take place in the appearance of the patient *pari passu* with the advance of the local disease of the thyroid gland and the result of treatment.

FIG. 8.

Four years after the commencement of the symptoms.

This case was kindly placed under my care by Mr. James Angus of Newcastle-on-Tyne, and although I have published Figs. 8 and 9 before I venture to reproduce them along with two earlier photographs of the same case for which I am indebted to my colleague Dr. Thomas Oliver. Fig. 8 was taken in 1883, four years after the symptoms first appeared in 1879. Fig. 9 was taken in 1890, showing a more advanced stage of the disease, and Fig. 10 in 1891 just before the treatment was commenced when the disease had already existed

[15] Brit. Med. Jour., March 24th, 1894, p. 618.

for 12 years. Fig. 11 was taken in 1892 after treatment for seven months and shows that the swelling has disappeared and a good growth of hair has taken place. As already mentioned, this patient died from mitral disease in 1897 when the thyroid gland was found to be entirely converted into fibrous tissue and fat as was shown in Fig. 7.

In addition to these very obvious signs of improvement the feeling of lassitude passes away and normal muscular strength and activity are regained. As a result of this those who before treatment could barely walk a mile are enabled to walk long distances, climb mountains, and under-

FIG. 9.

Eleven years after the onset of the disease.

take various other forms of exercise, mental processes become more active, the memory improves, and the hallucinations disappear. In some cases in which actual insanity had occurred it also has been cured. If albuminuria without actual renal disease has been present it disappears while the amount of urine is increased. The observations of Ord and White [16] show that the total amount of nitrogen eliminated is increased and that this increase is almost entirely due to the increase of

[16] Brit. Med. Jour., July 29th, 1893, p. 217.

urea in the urine. At first the amount of urea excreted may not only equal, but actually exceed, the normal average quantity. The number of red corpuscles in the blood increases. In patients who have not reached the menopause menstruation returns and takes place regularly even when there has been amenorrhœa for several years. In fact, the myxœdema is entirely cured though the fibrosis of the thyroid gland remains unaffected by the treatment.

FIG. 10.

At commencement of treatment when the disease had lasted for 12 years.

Treatment of Cretinism.

We have already considered the results of athyroidism in young animals and children and have seen how they are more serious than in the adult owing to the arrest of development. The treatment of a cretin consequently presents a more formidable task, but the results are in some respects even more interesting than those just

Fig. 11.

After treatment for seven months.

described. I would again point out the importance of carefully considering the possibility of the presence of disease or lack of development of the thyroid gland in every case of arrest or delay of development in children. In all such cases it is important to look for slight signs of cretinism. There are of course other causes of arrest of growth, such as achondroplasia, but I have seen several cases where the ordinary symptoms of cretinism were not distinct and might easily escape observation if not searched for carefully, in which the rapid improvement following thyroid treatment has proved that the arrest of development was due to thyroidal insufficiency. The importance of early diagnosis in such cases lies in the fact that the earlier the treatment is commenced the better prospect there is of normal development of the central nervous system. Experience has already shown that in cretinism of some years' duration rapid as the improvement in the physical condition may be the intellectual development is much slower, so that when treatment is commenced late it is doubtful if the latter will ever advance as far as when treatment is started early. If any doubt exists as to the diagnosis it is a good plan to carry out the treatment for one or two months. If no distinct improvement takes place the want of development is not due to cretinism, for in other forms of arrested growth the treatment has comparatively little effect though it is worthy of trial. The treatment of early cretinism is carried out on the same lines as the treatment of myxœdema in the adult. During the first stage gradually increasing doses of thyroid extract are given till the symptoms disappear. It is advisable in treating a small cretin to begin with a dose of one or two minims each evening, gradually increased by the addition of one minim each week or fortnight until a dose of five, seven, or 10 minims, according to the size of the child, is reached. As the child gets older it may be found necessary to increase the daily dose from time to time by the addition of another minim. If too large doses are given the pulse becomes too frequent, pains may be felt in the limbs and elsewhere, the temperature may rise above the normal level, and purging may follow. As in the adult the treatment must be continued as long as the patient lives. As soon as the symptoms have disappeared it is only necessary to determine the most suitable permanent dose and to ensure its uninterrupted administration.

In the treatment of cretinism which has lasted for some years we have a much more difficult task to perform, but very good results can be obtained. Even when the disease has already lasted 10 or 12 years, provided the patient is not more than 18 or 20 years old, a remarkable amount of growth can still take place. In these cases from three to five minims of thyroid extract may be given at the commencement and increased according to the progress observed. Even in cases in which the symptoms have lasted for 20 or 25 years some

growth and marked improvement in all the symptoms take place. In cases of long duration attacks of syncope are not uncommon. In such the earlier part of the treatment is

FIG. 12.

A, aged 28 years, June, 1895; height 34½ inches.

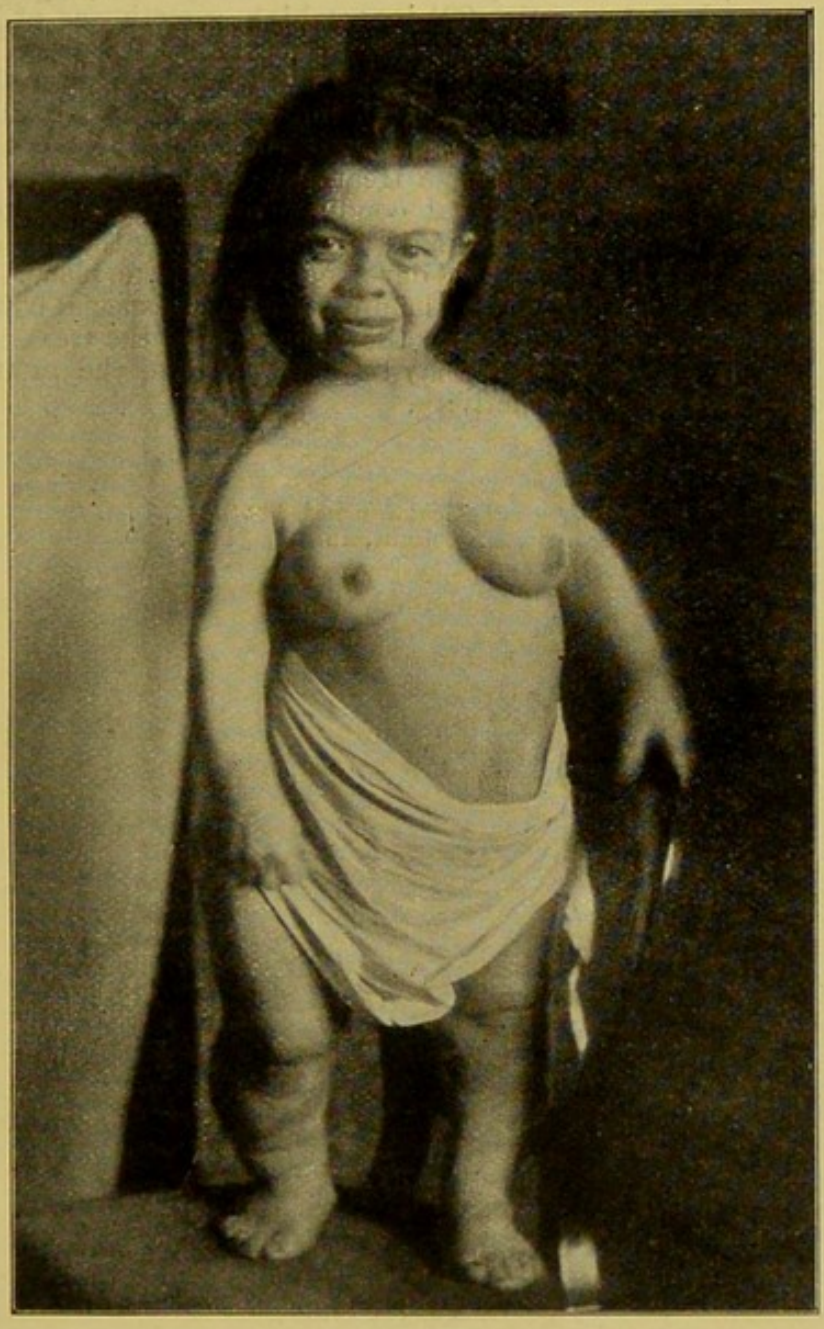
more safely accomplished by keeping the patient in bed and giving small doses of one or two minims only at first.

Results of the Treatment of Cretinism.

When the necessary stimulus to the normal metabolism of growth is thus supplied to a cretin in the early stages of the disease the symptoms disappear. The swelling gradually diminishes in all parts of the body. The tongue, lips, and nose diminish in size so that the appearance becomes natural. The skin becomes soft and moist and the temperature rises to normal. Growth which at this early stage will only have been partially arrested starts afresh. If the treatment is continuously carried on in such a case from the earliest time at which the disease is recognisable there seems no reason to doubt that ultimately the child will grow up into a fully-developed healthy adult who, however, would of course at any time develop symptoms of myxœdema if his supply of the extract was discontinued. The amount of improvement which may take place in very advanced cases is well illustrated by the further course of the case (A) described and shown in Fig. 12. In this case the symptoms had been present for some 27 years before treatment was commenced. The dose was at first one drop a day, and has been gradually increased till now she takes 15 drops, equal to about 12 minims of thyroid extract daily. At the commencement of the treatment growth had been arrested, apparently for many years, as she only measured 34½ inches in height. She now measures 38½ inches, having grown four inches in three and a half years. The hair is much less coarse than it used to be and the scalp is white and smooth. The swelling has greatly diminished so that the nose, cheeks, and lips are much smaller than they were and the whole expression is much more bright and intelligent. The mouth is kept closed and the tongue has become normal in size and no longer protrudes between the lips. The condition of the teeth does not seem to have improved except that she can now crack nuts which she was unable to do before. The elastic pads have disappeared from the supra-clavicular regions. A most remarkable development of the mammary glands, which before treatment were entirely undeveloped, has taken place. This is well shown in a recent photograph (Fig. 13) in which it will be seen that the nipples and breasts are now very well developed. Some pubic hairs have grown and menstruation which had only occurred very scantily on a few occasions is now regular and abundant. The abdomen is less prominent and the umbilicus is retracted. There is still marked lordosis. The skin is much less dry and perspires freely when she is walking. She is much more energetic and the muscular strength has increased so that she can now walk two miles. The temperature has long been normal. She is distinctly more intelligent, her vocabulary has increased, she can recognise people and animals, and can make her wants perfectly understood. She is unable, however, to frame a sentence and uses only single words, or

at most two or three together. She is careful and cleanly in her habits.

FIG. 13.



A, February, 1899 ; height 38½ inches.

This case is a good example of the amount of improvement of which even the worst cases are capable. Greater improvement still has been obtained in cases of some years'

duration in which the patients are still under 20 years of age. Thus in Dr. John Thomson's[17] patient, aged 18 years and eight months, 33½ inches in height, there was an increase in the height of four and three-eighth inches in 12 months; and in Dr. Byrom Bramwell's[18] patient, aged 16 years and four months, 29½ inches high, growth was at the rate of six and a half inches in six months.

The intellectual development is always much slower than the bodily growth and general improvement in all other respects. The shorter the duration of the symptoms has been at the commencement of the treatment the more rapid the improvement in the mental condition and I think it is only in cases in which the treatment is started early that we can expect normal intellectual development to take place. In cases of some duration it is important that a special education should be carried on at the same time as the treatment in order that the patient may be able to make the most of the renewed cerebral activity.

[17] Edinburgh Medical Journal, February, 1844.
[18] Brit. Med. Jour., Jan. 6th, 1894.

LECTURE III.[1]

Compensatory Hypertrophy.

Mr. President and Gentlemen,—The whole question of compensation and compensatory hypertrophy of organs in disease is of such great interest and practical importance to us that any facts which tend to throw light on the conditions under which they are developed are of value. In health we can by specially arranged exercises bring into operation the pathological law, that any muscle contracting intermittently against an increased resistance which it can overcome undergoes hypertrophy, and thus induce hypertrophy of the biceps or any other muscle. In some diseases our chief object is to favour and encourage compensating hypertrophy by every means in our power. In valvular disease of the heart adequate compensation in the form of "work hypertrophy" is of prime importance, the object of our treatment being to encourage and maintain its proper development and as long as possible ward off the disastrous effects of its failure. All hollow muscular organs develop compensatory muscular hypertrophy when their work is increased by some abnormal resistance to the expulsion of their contents which can be overcome by an extra effort. Other tissues also can undergo similar changes, an example of which is given by the condition of the blood in cyanosis. It has been shown by Toeniessen, Gibson,[2] and others that in the intense cyanosis of congenital heart disease the hæmoglobin is increased in amount and the red and white corpuscles are increased in number. The hæmoglobin may be increased up to 120 or 160 per cent. of the normal amount, the red corpuscles up to 9,000,000 (about double the normal number), and the white to 16,000 in each cubic millimetre of the blood. These changes may fairly be regarded as indicating a compensating hypertrophy of the blood which enables it to carry more oxygen in face of the adverse conditions under which the circulation is carried on. Marie regards a similar increase in the number of the red corpuscles which occurs in those who live at high altitudes as a similar compensation. The

[1] Delivered on March 14th, 1899.
[2] The Lancet, Jan. 5th, 1895.

glandular organs of the body have also remarkable powers of development under the influence of appropriate stimuli, as, for example, the development of the mammary glands during pregnancy. Both secretory and excretory glands can undergo compensatory hypertrophy when a portion of the gland has been disabled by disease or design in such a manner as to throw an increased amount of work upon the remainder. The stimulus of working at higher pressure than normal here as in the heart leads to a development of a compensatory hypertrophy, such, for example, as is seen in one kidney after the removal or destruction by disease of the other.

It is important in all cases to ascertain the minute structure of organs which have thus developed a compensatory hypertrophy for it is not necessarily a simple hyperplasia or exact reproduction of the normal structure. In the kidney Larazus-Barlow[3] states that there is hyperplasia of the cells and hypertrophy of the glomeruli, and he quotes Eckhart's statement that if the hypertrophy is the result of congenital absence of one kidney there is both hypertrophy and hyperplasia of both glomeruli and tubes ; if later in life one kidney is destroyed or removed hypertrophy without hyperplasia of either glomeruli or tubes is found in the other. Owing to the special anatomical position and physiological properties of the thyroid gland it affords unusual facilities for observing some of the phenomena of compensatory hypertrophy. It is now a well-known fact owing to the work of Horsley,[4] Halsted,[5] and Edmunds[6] that when a portion of the gland is removed the remainder undergoes compensatory changes in virtue of which it is enabled to supply enough secretion to prevent the appearance of the symptoms of athyroidism. The portion removed at one time may be one-half or even three-quarters of the whole gland and Halsted has shown in the dog that successive portions, if removed on three or four separate occasions, may be excised until only one-eighth or even one-sixteenth of the original gland is left without symptoms of athyroidism being developed, so great is the power of undergoing compensatory hypertrophy. Although these changes are accompanied by an increase in size the hypertrophied remainder does not attain the size of the original gland, so that weight for weight it has to do more work than the original glandular tissue. Under these circumstances it is not so surprising that the structure of a piece of the gland which has undergone compensatory hypertrophy should differ somewhat from that of the normal gland. And this we find to be the case, for when sufficient hypertrophy has developed to supply as much secretion as is necessary we do not find a simple hyperplasia of the original glandular tissue but considerable change in structure throughout. The alveoli instead of being nearly circular become irregular in

[3] Manual of General Pathology, p. 537.
[4] Brit. Med. Jour., Dec. 5th, 1896.
[5] Johns Hopkins Hospital Reports, 1896.
[6] Journal of Pathology January, 1898.

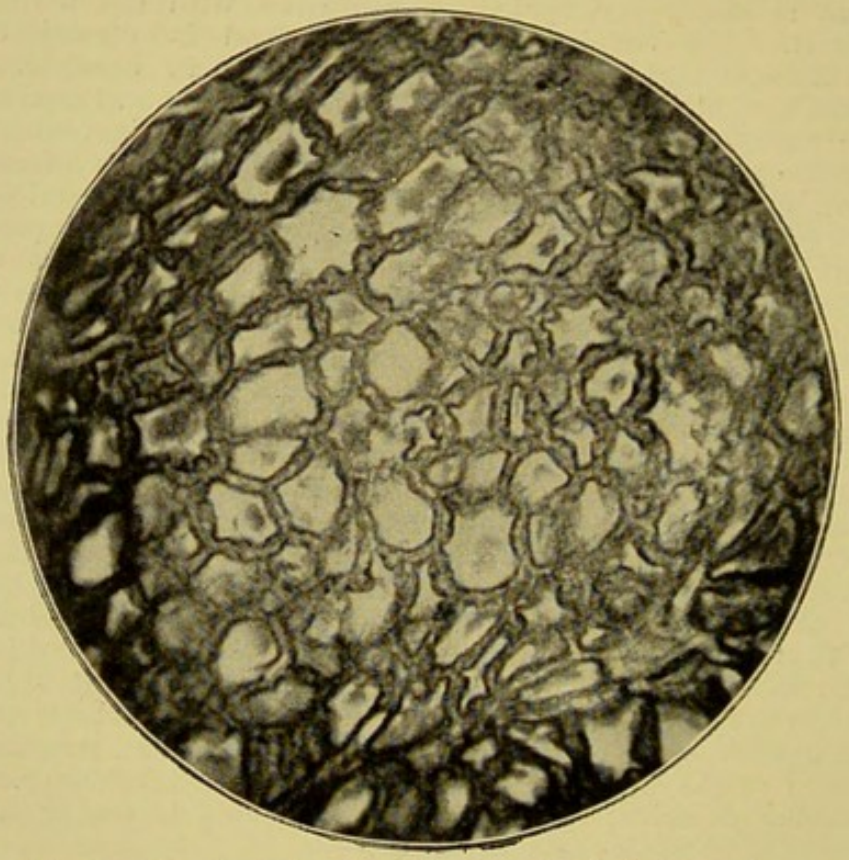
outline. This change is due to the folding of the wall which projects at different points into the lumen of the alveolus. In advanced hypertrophy the lumen may appear to be star-shaped or it may be almost obliterated by neighbouring folds of epithelium coming into contact. The appearance in laces may then closely resemble that of a racemose gland. The epithelial cells themselves are also altered. They are considerably increased in size, the ordinary low cubical epithelial cells being converted into tall columnar cells. The result of these two changes is that in equal areas the secreting cells are greatly increased both in numbers and size in the hypertrophied as compared with the normal gland. The colloid lying in the gland is diminished in amount and appears to be more watery in consistence than normal. This change in consistence cannot, however, be accompanied by any deficiency in the active ingredients of the secretion as it is able to prevent the onset of any symptoms of athyroidism. The appearances just described are evidently those of glandular tissue working at high pressure and just able to supply the necessary amount of secretion without storing any in reserve in the alveoli as is usual in the normal gland.

In illustration of these changes I may refer to an experiment in which I removed the whole of the left lobe and the greater part of the right from a rhesus monkey. After the operation there was slight hebetude and harshness of the voice. No other symptoms developed although the animal was kept under observation for 14 months and then was killed as it contracted general tuberculosis. A piece of glandular tissue which had developed from the small portion of the right lobe left at the operation was found, weighing 0·42 gramme. Fig. 14 shows the changes in structure which had taken place. The folding of the epithelium giving a larger secreting surface is clearly seen and in some of the smaller alveoli near the centre the consequent irregular shape of the lumen is evident. The epithelial cells have become columnar in type while the colloid is scanty and seems to be watery in consistence.

The remarkable results which have been shown by Dr. Rose Bradford to follow the excision of a portion of the kidney and which were so well described by him in his Goulstonian Lectures last year raise the question as to whether these changes in the structure of the thyroid are due entirely to the wants of the body acting as a stimulus to the compensatory growth of the gland or whether they are in any way due to some other local or general effect of the operation itself. If the compensating growth of the one lobe takes place simply in response to a call for more secretion to make good the loss of the other lobe no hypertrophy should take place if this want is fully supplied from other sources. This point may be tested by removing one lobe of the gland and giving thyroid secretion continuously for some time and then removing the other lobe for examination. If no changes indicating compensatory

hypertrophy are found in the second lobe it goes far to show that the hypertrophy develops simply as the result of an insufficient amount of thyroid secretion being present in the blood. To test this point the right lobe and parathyroid were removed from a male bonnet monkey. For the next three weeks 12 minims of thyroid extract were given in the course of each week. Then as the animal became rather emaciated the quantity was reduced to half this amount for the next five weeks.

FIG. 14.



Compensatory hypertrophy of the thyroid gland of a monkey, showing plication of alveolar wall, scanty colloid and columnar epithelium.

Slight myxœdematous symptoms then appeared, but they diminished on increasing the dose to 24 minims in the week ; this was continued for two and a half weeks when the animal died from dysentery. The left lobe was found to be pale in colour and only weighed 0·03 gramme. No parathyroid was found attached to it. Microscopical sections showed no signs of compensating hypertrophy even in its earliest stages. In another experiment the right lobe and parathyroid were removed and one minim *per diem* of thyroid extract was given by the mouth for 16 weeks and then the left lobe and parathyroid were removed. The right lobe with

the parathyroid which was removed first weighed 0·3 gramme and was found to be abnormal in structure to start with, as it resembled a hypertrophied gland in structure. Similar appearances were found by Halsted in the thyroid gland of several healthy dogs. The occasional occurrence of such changes in apparently healthy animals is at present difficult to explain. The interesting point in this case is that after the prolonged interval of 16 weeks during which the extract was given the left lobe was found to be paler in colour and it weighed 0·25 gramme. The microscopical structure was normal and showed no signs of commencing compensatory hypertrophy. If this lobe was originally in the same condition as the right the treatment seems to have restored it to a normal condition, and if not it at any rate showed no signs of compensating hypertrophy. As far as they go these experiments tend to show that if the proper amount of secretion is supplied after the removal of one lobe compensating changes do not take place in the other.

In connexion with this part of the subject I have tried the effect of prolonged administration of thyroid extract upon the healthy thyroid gland. It is well known that parenchymatous goitres often decrease in size when treated by thyroid extract. One explanation of this result is that a partial atrophy from disuse is established when the full amount of secretion is supplied from an external source. Two experiments have been made to ascertain if any atrophic changes could be induced in the healthy thyroid gland by supplying secretion ready made, as it were, and so doing away with the normal stimulus to secretion. The thymus atrophies after the first year of life from disuse and the thyroid does so itself in old age possibly for the same reason.

A small bonnet monkey was given one minim of thyroid extract *per diem* by the mouth for 44 days and then three minims for 31 days. The thyroid gland was then removed. It looked small and pale in colour and with the two parathyroids weighed 0·11 gramme. The microscopical appearance of the gland was normal, the epithelial cells and their nuclei being stained as usual and the alveoli were well filled with secretion. In another similar experiment a male bonnet monkey was given one minim of thyroid extract for 44 days and three minims daily for 42 days. The thyroid gland was then removed and with the parathyroids weighed 0·14 gramme. The nuclei were all stained and the alveoli were well filled with secretion. There was rather more fibrous tissue in the interalveolar spaces than is generally seen in the normal gland, but not a sufficiently well-marked increase to amount to a pathological change. The glands were certainly pale in colour and light in weight and appeared to have undergone some diminution in size, but no evidence of atrophic changes was found in the microscopical specimens. Possibly if larger doses had been given for a longer period some more definite change in the structure of the gland might have been found.

Goitre.

The pathology of goitre is a subject of much importance for the disease is still endemic in this country in the valleys which drain the Pennine Range of hills east and west from the Border as far south as the Peak in Derbyshire. Time will not permit me to discuss the origin of endemic and sporadic goitre, but I wish to draw attention to the interesting effects which have followed the treatment of simple parenchymatous goitre by thyroid extract. At first sight such treatment may seem somewhat superfluous, but experience has shown, and to that of others I can add my own, that this method of treatment frequently leads to a notable diminution in the size of the goitre. Adenomata, cystic adenomata, and other new growths are not influenced by the treatment though the parenchymatous enlargement which often accompanies them may be diminished. In the treatment of goitre it is advisable to begin with 10 minims of liquor thyroidei each night. In the course of a few days if the pulse is not accelerated beyond 90 or 100 this dose may be given twice and at the end of a week thrice daily. If well borne the dose may be still further increased. The treatment should be continued for three or four weeks to give it a fair trial and longer if the goitre continues to decrease in size. In several cases in which the general enlargement of the gland has been sufficient to cause dyspnœa by compressing the trachea, so that an operation had to be considered, the gland has been reduced to two-thirds or even one-half of its former size and all the symptoms of pressure removed and with them the necessity for an operation. The beneficial effects of this treatment may be due to the iodine which is present in combination with a proteid in thyroid extract, for iodine has long been used with good results in the treatment of goitre. We have seen that the healthy thyroid of the monkey showed some signs of diminution in size under the same treatment and I would suggest that the decrease in size in goitre may be due to part of the enlarged gland passing into a resting condition and consequent diminution in size if there is not an actual disuse atrophy as a result of the treatment.

Exophthalmic Goitre.

Exophthalmic goitre, with its many varying phases, is a disease of great interest from several points of view. The various clinical types in which it comes before us and the great difficulties in treatment which it often presents render a true solution of the problem of its pathology of the greatest importance. The circulatory and nervous systems have each in turn been considered to be at fault, and it is only recently that attention has been drawn to the important part which is played by the thyroid gland in the pathology of the disease. The central and sympathetic nervous systems have been carefully

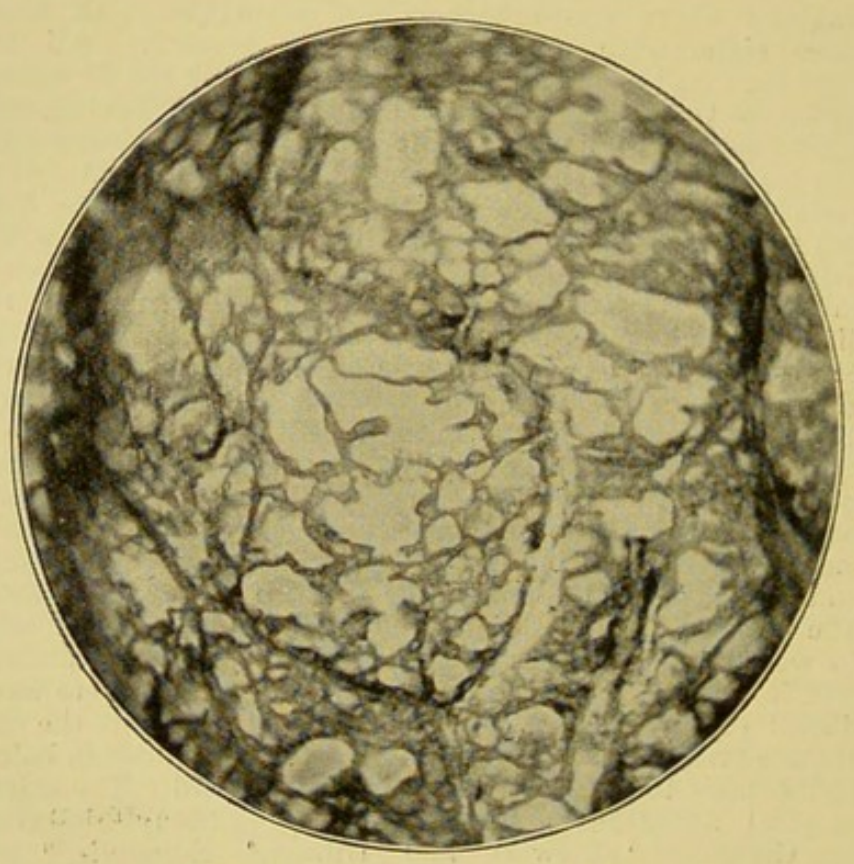
examined in a considerable number of cases; in some they have been found quite normal, in others various lesions have been described, but these have varied in different cases and on the whole appear to be rather secondary than primary in origin. I shall not describe the various lesions which have been found, as I have already elsewhere[7] discussed their relative importance. The lesions found in the thyroid gland are far more constant in character than any yet described in the nervous system and it is the most obviously diseased organ to be found in a case of exophthalmic goitre. In nearly all cases of exophthalmic goitre there is a palpable enlargement of the thyroid gland. On looking through my case-books I find notes on 70 cases of exophthalmic goitre which I have seen during the last nine years in the North of England where the disease is not uncommon. Of these cases eight were men and 62 were women. All the eight men had enlargement of the thyroid; of the 62 women all except three had enlarged thyroid glands. Taking both sexes together we find that only 4·3 per cent. of these cases had no goitre. It has been shown by Maude that in some cases enlargement of the gland may be present at one time and not at another, so that even in those three cases which were only seen a few times there may have been some enlargement at some other time during the course of the disease which had escaped observation. In any case, in 95 per cent. of my cases there was either enlargement of the gland at the time when the case was seen or there was a distinct history of enlargement at an earlier stage.

The enlargement of the thyroid gland in exophthalmic goitre is as a rule uniform. In cases of long duration it may be irregular in shape and consistence owing to the development of fibrosis leading to the formation of irregular strands and masses of hard fibrous tissue in some parts of the gland. The veins on the surface are large and their walls are thin. In well-developed cases the goitre is very vascular and the arteries are dilated and tortuous, indicating that there was a liberal supply of blood during life. On section the cut surface presents a uniform appearance; it is lighter in colour and exudes less colloid than a normal gland. The microscopical appearances have been very clearly described by Greenfield,[8] Stewart and Gibson,[9] Edmunds,[10] and Abram.[11] The general appearance is that of a gland in a state of great secretory activity and has been aptly compared by Greenfield to that of the mammary gland during lactation. The number of alveoli is not only increased by the total increase in size of the gland but in equal areas more secreting tissue is seen than in the normal gland. In many places the lumen of the alveolus is irregular in outline owing to folds of the alveolar wall covered with epithelium pro-

[7] Twentieth Century Practice of Medicine, vol. iv.
[8] The Lancet, Dec. 16th and 23rd, 1893.
[9] Edinburgh Hospital Reports, vol. i.
[10] Transactions of the Pathological Society of London, 1895.
[11] The Lancet, Nov. 16th, 1895.

jecting into it, so that even when the gland is but slightly enlarged there is a marked increase in the amount of the secretory epithelium. The lumen of the alveolus is in consequence diminished in size in some cases to a considerable extent. The actively secreting part of the gland is thus increased at the expense of the storage room which is so ample in the normal gland. The epithelium which lines the alveoli and covers these folds is changed in type, for the cells instead of being flat or cubical are tall and columnar. There is less secretion to be seen lying in the alveoli than in health. This diminution in quantity is

FIG. 15.

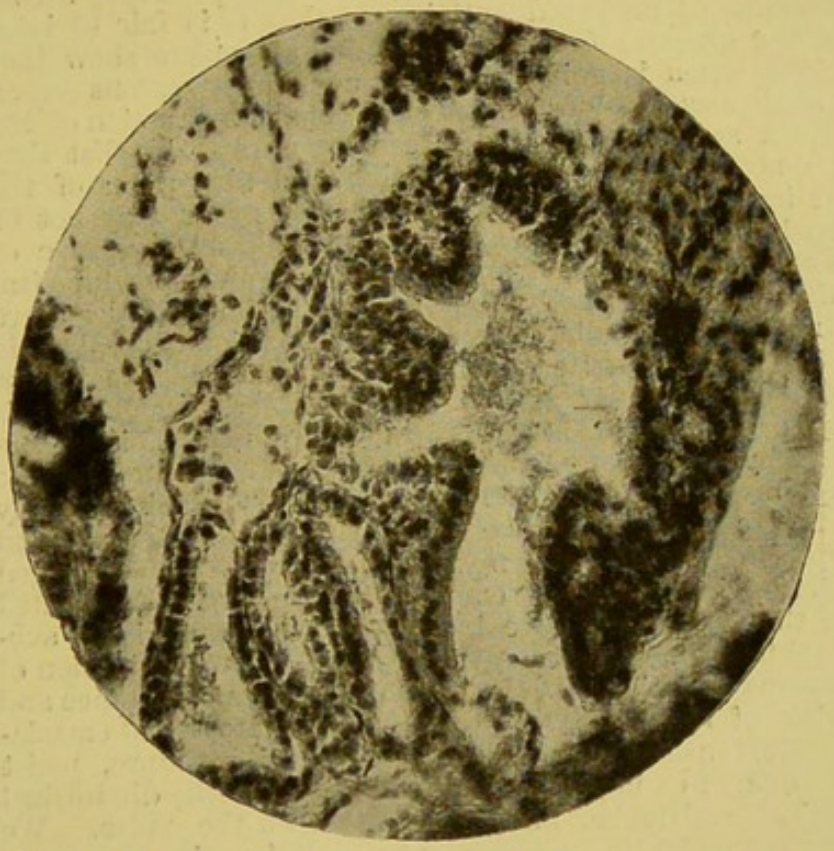


Exophthalmic goitre. Low power.

partly due to the decrease in the amount of storage room. In addition to this, however, the alveoli are only partially filled, an appearance which suggests that there is a more rapid removal of the secretion from the gland than in health. The colloid is also more watery in consistence and it stains less deeply than normal. Eosine does not stain it at all and Renant considers that it resembles fœtal colloid more nearly than that found in the healthy adult. These changes are well shown in two specimens from cases which have been under my care. The section shown in Fig. 15 was taken from the right lobe of the thyroid gland

of a married woman, aged 32 years, who had suffered from attacks of palpitation for several years. There had been enlargement of the thyroid for a year, exophthalmos for nine months, and progressive emaciation for eight months. The pulse varied from 120 to 140. As medical treatment failed to arrest the progress of the disease the right lobe was removed by Mr. F. Page. Unfortunately the patient died suddenly an hour after the operation. This specimen shows the general appearance of the gland under a low power, the plication of the alveolar wall, and the diminution in the amount of secretion in the alveoli.

FIG. 16



Exophthalmic goitre, showing plication of alveolar wall, scanty colloid and columnar epithelium. High power.

Fig. 16 and Fig. 17, which were also photographed by Dr. R. A. Bolam, were taken from sections prepared by my research clerk, Mr. J. Muirhead. The specimen shown in Fig. 16 was taken from a man, aged 30 years, who had suffered from acute exophthalmic goitre for some four or five months. There had been goitre, great nervousness, exophthalmos with retraction of the upper eyelids and von Graefe's sign, frequent pulse, rapid respiration, emaciation, sweating, and diarrhœa. In addition he had an attack of appendicitis followed by the formation of a small

abscess which contributed to the early fatal termination. This specimen shows an alveolus under a high power in which the changes described are well-marked. There are several deep folds in the wall, the columnar type of the epithelium is clearly seen, and only a small amount of lightly stained secretion is lying in the irregularly shaped lumen.

From the above description and illustrations it will be seen that the structure of the gland in exophthalmic goitre resembles that in compensatory hypertrophy in a remarkable manner. In both there is the increase in the secreting structures, as shown by the plication of the alveolar wall; in both the epithelium is changed from a cubical into a columnar type, while the secretion stored in the alveoli is less in quantity and more watery in consistence. We know that the changes in compensatory hypertrophy are an indication of increased activity, so that it is fair to infer that the changes found in exophthalmic goitre show that hypersecretion is going on. For additional reasons which we shall now consider the most rational explanation of the complex symptoms of this disease appears to be that they are due to an excessive formation and absorption of the secretion of the thyroid gland which may or may not be altered in composition and to the constant presence of this excess in the blood and its action upon the metabolism of the tissues generally, but more especially of the nerve centres in the medulla. According to this view exophthalmic goitre is the opposite condition to myxœdema, the former being the result of excess as the latter undoubtedly is of lack of thyroid secretion in the blood. This is supported by the strong contrast which is presented by the symptoms of the two diseases, a contrast which is nearly as marked as that between the small fibrous and atrophied gland of myxœdema and the enlarged hypertrophied gland of exophthalmic goitre. Associated with the former we have increase of weight, stolidity, subnormal temperature, dryness of the skin due to diminution of cutaneous secretion, with increase of electrical resistance and slowing of the pulse, while with the latter we find emaciation, nervousness, normal or raised temperature, moist skin due to increase of secretion, with diminished electrical resistance, and acceleration of the pulse. We may conveniently express the relationship of myxœdema and exophthalmic goitre in their various degrees of severity in the following diagrammatic manner. If we take 100 as representing the normal amount of thyroid secretion of health then 75 per cent. is probably about the amount of secretion found in these cases of early thyroidal fibrosis with slight myxœdema to which I have already alluded. If half the glandular tissue is destroyed and only 50 per cent. of secretion is formed the symptoms will be moderate; if 25 per cent. the symptoms will be well-marked; and if none at all is formed they will be severe, as in the advanced case shown in Fig. 10 (see THE LANCET of March 11th, p. 676). In the reverse way in exophthalmic

goitre 125 per cent. of secretion would be present in a slight case, 150 per cent. in a moderate one, 175 per cent. in a well-marked one, and 200 per cent. in a severe case.

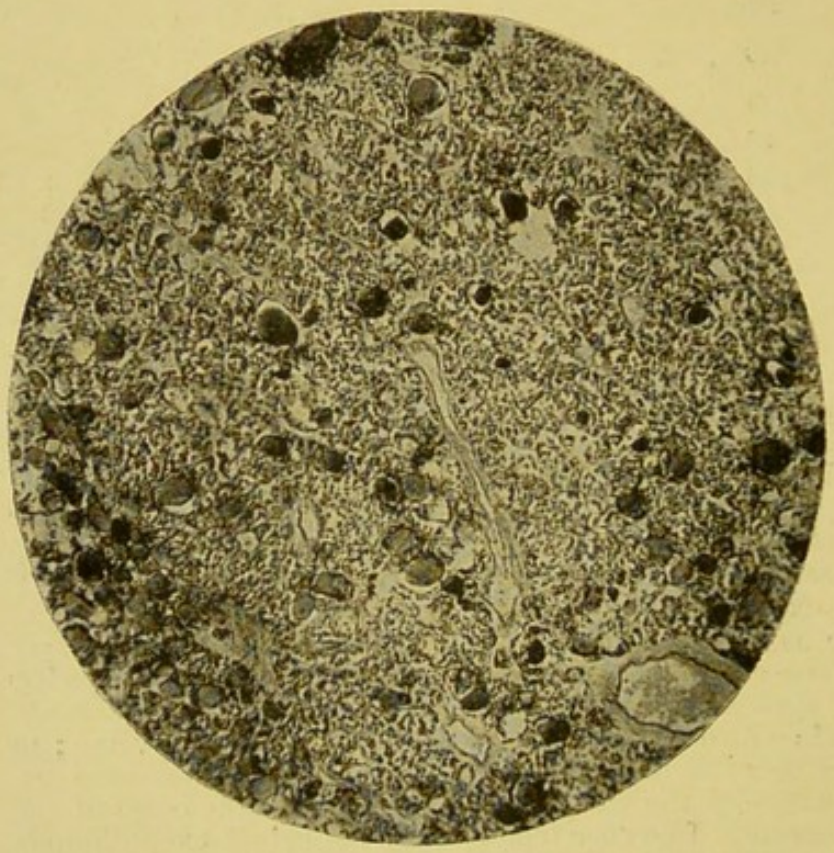
Percentage of thyroid secretion in the blood.	Degree of severity of the symptoms.
200 per cent.	Severe exophthalmic goitre.
175 ,, ,,	Well-marked ,, ,,
150 ,, ,,	Moderate ,, ,,
125 ,, ,,	Slight ,, ,,
100 ,, ,,	*Health.*
75 ,, ,,	Slight myxœdema.
50 ,, ,,	Moderate ,,
25 ,, ,,	Well-marked ,,
—	Severe ,,

In the case of myxœdema these percentages are in all probability approximately correct. In exophthalmic goitre, however, we have no means of ascertaining how much is actually formed. It may amount to much more than double the normal quantity in a severe case so that these percentages are purely relative and must not be taken to indicate the actual amount of secretion present in the blood. Another interesting point in the relationship between the two diseases is the repeatedly observed fact that recovery from exophthalmic goitre may be followed by myxœdema, while as far as I am aware exophthalmic goitre has never been observed to develop in a patient already suffering from myxœdema. In some cases the symptoms of exophthalmic goitre diminish as those of myxœdema develop; in others there is an interval of good health between the disappearance of the exophthalmic goitre and the onset of the myxœdema. In a case recorded by Baldwin[12] exophthalmic goitre developed in 1887 and recovery took place the following year. Two years after, in 1890, myxœdema developed which three years later was successfully dealt with by the thyroid treatment. In a similar case recorded by Joffroy and Achard and quoted by Möbius[13] the exophthalmic goitre existed for 23 years and then subsided to be followed by myxœdema. After death the nervous system was found to be quite normal and the thyroid gland in an advanced stage of fibrosis with atrophy. It thus seems evident that the development of thyroidal fibrosis in exophthalmic goitre by lessening the over-activity of the gland leads to a subsidence of the symptoms which, if the fibrosis and atrophy progress far enough, are replaced by those of

[12] The Lancet, Jan. 19th, 1895, p. 145.
[13] Die Basedow'sche Krankheit, p. 63.

myxœdema. Fig. 17 shows a section of the gland from an old-standing case of exophthalmic goitre. In this the alveoli are much diminished in number and between them there is a large amount of young cellular fibrous tissue. No symptoms of myxœdema were present at the time this patient died, but it is evident that if the fibrosis had advanced much further symptoms of myxœdema would have developed. While these changes are taking place in the gland the symptoms may pass from those of severe exophthalmic goitre through all

FIG. 17.



Exophthalmic goitre, showing diminished number of alveoli and large amount of young cellular fibrous tissue.

the stages mentioned in the table to those of severe myxœdema. One or two cases have been recorded in which the symptoms of myxœdema are said to have coexisted with those of exophthalmic goitre. The reasons for asserting the coexistence of the two diseases seem to be rather slender and to be largely founded on the presence of an irregular brawny swelling together with the symptoms of exophthalmic goitre. I have occasionally seen a firm subcutaneous swelling in some parts of the body in exophthalmic goitre but it certainly was not myxœdematous. It is important to have such cases carefully reported so

that more information may be obtained on this point. The persistence for a time of a few symptoms of exophthalmic goitre in a case of long duration which was passing into myxœdema is not unlikely, for the effects of the long-continued action of an excess of secretion on the nerve centres in the medulla may easily remain for a time even after the thyroid had begun to atrophy, just as the effects of the action of lead or the toxins of diphtheria on the nervous system persist long after the original cause has ceased to act.

The physiological effects of thyroid secretion in large doses are of special interest in this connexion. Exophthalmic goitre, though rare in the lower animals, has been observed in the horse, the cow, and the dog, so that if the right cause is brought into operation there should be no great difficulty in producing the disease in one of these animals. As we are ignorant of the causes of the change in structure and activity of the thyroid gland in exophthalmic goitre attempts can only be made to reproduce the symptoms we believe to be secondary to the excessive activity of the thyroid. This might be done either by grafting an excess of thyroid gland tissue into an animal or more certainly by feeding it with large quantities of thyroid secretion or by injecting it beneath the skin. Ballet and Enriquez [14] by feeding dogs with the thyroid glands of sheep produced distinctive symptoms in three out of six cases. These symptoms were elevation of temperature, tachycardia, tremors, conjunctivitis, emaciation, and in one animal quite distinct exophthalmos. Still more important are the results which have been observed to follow large doses of thyroid extract in man—a condition of thyroidism which seems to be more easily produced in those who have recovered from myxœdema than in those who have normal thyroid glands. It may develop rapidly if large doses are given or more slowly if smaller but still excessive doses are given for a long period. The earliest and most common symptom is increased frequency of the pulse. The patient complains of palpitation and the heart beats violently—100, 120, or 130 times a minute. A fine tremor of the hands is often present and the skin is flushed and moist. If the large doses are continued for some time emaciation also takes place. In addition to these symptoms elevation of temperature, restlessness, loss of sleep, polyuria, albuminuria, glycosuria, partial paraplegia, sensation of heat, and diarrhœa, all of which are occasional symptoms of exophthalmic goitre, have been recorded. In one remarkable case Béclère [15] observed exophthalmos and rapid respiration, in addition to other symptoms among those already mentioned, in a woman who had suffered from myxœdema and had taken 92 grammes of thyroid gland in 11 days.

Some remarkable toxic symptoms have been observed in

[14] La Semaine Médicale, xiv., 66, 1894.
[15] Ibid., 1894, p. 101.

some cases by Horsley and Rodocanachi,[16] Paul,[17] and other surgeons to follow partial removal of the enlarged thyroid gland. The most common symptoms which have been observed are fever, great frequency of the pulse, amounting to 150 or even 180 beats in the minute, rapid respiration, and great restlessness. In some of the cases the termination has been fatal at the end of a few days. As far as I am aware such symptoms have not been observed after a total thyroidectomy, so that they are not a result of the operation itself. The symptoms have occurred in cases of exophthalmic or soft parenchymatous goitre after removal of one lobe of the enlarged gland, and especially when it has been much handled or squeezed during the operation. In several cases a profuse flow of thyroid secretion has been observed to take place after the operation from the divided isthmus into the wound. The symptoms are similar to those which occur in acute cases of exophthalmic goitre and in thyroidism artificially produced in the manner already described and are evidently due to absorption from the wound of thyroid secretion poured out from the cut surface of the gland or to a large quantity of it being squeezed during the operation into the lymphatics and so into the blood stream. This absorption of the secretion is a source of real danger in operations for goitre and especially in cases of exophthalmic goitre. If, however, the gland is handled as little as possible during the operation, the cut surface is sealed by the cautery, and a free exit is provided for any secretion which may find its way into the wound, such symptoms will in all probability but seldom arise.

It is now well known that thyroid extract has a bad effect on patients with exophthalmic goitre. Under its influence the pulse becomes more frequent and the other symptoms are increased. In some instances where other treatment had been followed by marked improvement the administration of thyroid extract has been followed by a relapse into the former condition. In my opinion it should never be given in exophthalmic goitre as it is only adding fuel to the fire. The results of surgical treatment of exophthalmic goitre undertaken with the object of reducing the amount of secreting tissue by removal of one lobe, or of inducing atrophy by ligature of some of the arteries which supply the gland, are of great interest. Unfortunately, the operation itself though sound in principle is at present by no means free from risk. The steady improvement, however, which has resulted in many cases in which it has been successfully performed affords still further evidence that the symptoms of exophthalmic goitre are due to the over-activity of the thyroid gland.

It is a fact of considerable interest that along with the enlargement of the thyroid gland in exophthalmic goitre

[16] The Lancet, Oct. 9th, 1897.
[17] Brit. Med. Jour., Jan. 1st, 1898.

other ductless glands may be increased in size. The thymus gland is very often enlarged; in all the cases recently examined at St. Thomas's Hospital Dr. H. Mackenzie[18] has found the thymus persistent and enlarged, the microscopical structure being normal. Exophthalmic goitre and acromegaly are sometimes found to occur together. I have recorded two examples of this and collected records of three others.[19] In acromegaly the pituitary gland is enlarged and the enlargement seems to be analogous to that of the thyroid in exophthalmic goitre, so that we have the remarkable fact that all these three ductless glands may be simultaneously enlarged. We know no explanation of this but it suggests that possibly some common factor may be the cause of the enlargement. That some association exists between the thyroid and pituitary glands is further shown by the enlargement which takes place in the latter when the former is removed or disabled by disease.

These facts all indicate that in the treatment of exophthalmic goitre attention should be directed to the thyroid gland. Time will not permit me to discuss the question of operative treatment, but there can be little doubt that removal of part of the enlarged gland is a rational method of treatment and when the risks of the operation are diminished it should be more frequently employed in severe cases in which medical treatment has failed to do good. Of medical treatment much has been written. In my own cases inunction of red iodide of mercury ointment over the goitre and belladonna given in large doses internally so as to check the hypersecretion of the gland have been of most service. If the palpitation is excessive convallaria has proved more useful than any other member of the same group of drugs. Where there has been great nervousness the bromides have done good. In only one case have I seen decidedly good effects from taking thymus. In this case three tablets of dried thymus were taken each day for nine months, for the last six and a half of which the red iodide of mercury was used as well. As a result of this treatment the pulse-rate, which varied from 132 to 143, fell to 84; the thyroid gland, which had been considerably enlarged, returned to its normal size; the tremor became much less; and the exophthalmos was diminished.

In conclusion, Mr. President and gentlemen, allow me to thank you for the kind help which you have given me by your attention in my endeavour to place before you some of the facts which help to explain the function of the thyroid gland and the practical uses to which such knowledge can be put in the treatment of disease, and I trust that the wishes of the founder of this lectureship have thus been carried out in the spirit, if not in the actual letter of his bequest.

[18] Allbutt's System of Medicine, vol. iv., p. 503.
[19] Edinburgh Medical Journal, 1897, p. 170.

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