THE GOULSTONIAN LECTURES ON THE PATHOLOGY OF THE THYROID GLAND.*

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LECTURE I.

MR. PRESIDENT AND GENTLEMEN,—I must, in the first place, thank you very sincerely for the honour 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 the 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 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 which follow when this function is diminished or lost by excision 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 knowledge 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 thyroglossal 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 be-

come hollowed out by the accumulation of the colloid substance which is secreted by the epithelial cells into the lumen of the alveolus.

His¹ has found that in some cases the thyroglossal 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,² who examined a hundred 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 connection with the pharynx is still maintained. Andriezen³ directed attention to the fact that the thyroid gland is represented in ascidians by a mass of glandular tissue, and in amphioxus by a hypobranchial 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 history 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, 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 brown-red colour. It usually weighs from an ounce to an ounce and a-half (30 to 50 grams). It is relatively larger in the infant than in the adult, thus Huschke and Weibgen⁴ found that in newborn children the weight of the gland was equal to from $\frac{1}{100}$ to $\frac{1}{50}$, and in adults from $\frac{1}{1225}$ to $\frac{1}{1500}$ of the total weight of the body. The gland is as a rule somewhat larger in women than in men, though Ewald⁵ makes a contrary statement supported by Weibgen, who gives the average weight in the male as 34.2 grams and in the female as 29.7 grams. Each lobe is about 2 inches (50 mm.) long, $1\frac{1}{4}$ inch (30 mm.) broad, and $\frac{3}{4}$ inch (18 mm.) deep. The right is generally a little larger than the left. The isthmus is about $\frac{1}{2}$ inch (12 mm.) broad and $\frac{1}{4}$ to $\frac{3}{4}$ 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 inferior thyroid arteries on each side, and in some cases

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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 are in close proximity to the base 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 and shape. In 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 with secretion. No basement membrane to this epithelium has been described. Two kinds of cells are found in this epithelium, the chief cells, and the colloid cells. The chief cells are usually cylindrical, sometimes cubical in shape. They measure from 8 to 16 μ in height and from 6 to 8 μ in breadth, while the nucleus, which is round, measures from 5 to 6 μ in diameter. The colloid cells are considerably shorter than the chief cells, thus Hürthle⁶ found in one specimen that while the chief cells measured 12 to 14 μ in height, the colloid cells were only 7 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 Figs. 1 and 2, which are taken from transverse sections through the lateral lobe of the thyroid gland of a bonnet monkey. This and the other microphotographs, which will be shown later, have been kindly prepared from my specimens by Dr. R. A. Bolam. This illustration also shows how closely in this animal the parathyroid is attached to the thyroid gland, in which it may even be 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 gland 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 either the lymphatics or the veins. The evidence we possess shows that the former is the usual path, for it was shown by King and by Horsley⁷ 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 wall 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 the growth of 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, 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 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 secretion varies according to circumstances. Of these, however, we possess but little information. Stimulation of the laryngeal nerves or of the sympathetic with the faradic current produces no change indicative of increased secretion. Pilocarpin produces a marked increase in the secretion of the colloid, as was 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 myxoedema.

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 constituents of it. Notkin⁸ regards thyreoproteid, a substance which he isolated from the gland, as an active constituent which behaves like an enzyme. Gourlay⁹ 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 Roos¹⁰ made the important discovery that the colloid substance contains iodine in an organic combination with proteid which they named "thyroidin." This substance contains 9.3 per cent. of iodine, and 0.56 per cent. of phosphorus.

Hutchison¹¹ has found that two proteids are contained in the gland—a nucleo-albumin, which is contained in the epithelial cells and the 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 is non-proteid, contains more iodine and all the phosphorus of the original colloid, and is more active in removing symptoms due to loss of thyroid secretion than the proteid portion. S. Fraenkel¹² obtained a crystalline substance with the formula $C_6H_{11}N_3O_2$ 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 Gley¹³ that removal of the parathyroid glands along with the thyroid gland produced different effects to 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, dilatation of the pupils, and rise of temperature. Removal of the thyroid gland alone was followed by no such immediate effects.

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 eleven months in one case and twelve 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 to that described by Gley after removal of the parathyroids as well. These slides show you the appearance of one of these animals killed eleven months after the operation, and the ears of the other killed twenty-one months after. The ears were very dry, and 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 $\frac{1}{4}$ in. In

many places this dried margin had broken off, leaving an irregular outline to the ear. In a third rabbit, which was kept for twenty-seven 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 gram, or about one-third the weight of a complete gland, 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 forty years ago Schiff showed that dogs did not long survive the operation, and in 1884 he found that fifty-nine out of sixty 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 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 dyspnoea 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 subnormal before death. The red corpuscles are diminished and the white increased in number. Very similar symptoms occur in cats. The observations of Vassale and Generali¹⁴ on cats and dogs, of Edmunds¹⁵ on dogs, and of Welsh¹⁶ 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 parathyroid 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,¹⁷ and myself. In the bonnet monkey (*macacus sinicus*), which I have used, with one exception, in all my experiments, a parathyroid gland lies in close connection with, or actually embedded in, each lobe of the thyroid gland, as is shown in Figs. 1 and 2. As a result of this, when the thyroid gland is removed

Fig. 1.—Transverse section of thyroid gland of bonnet monkey showing structure and close attachment of parathyroid gland.

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 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.

Fig. 2. Transverse section of thyroid and parathyroid glands of monkey showing one portion of parathyroid at lower edge of section, and another kite-shaped portion just to the left of the centre of the section. Low power.

I have removed the whole or a part of the thyroid gland in nine bonnet monkeys and one rhesus monkey, in four of the former the symptoms were allowed to develop with the object of testing the influences 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 a 1 in 1,000 solution of perchloride of mercury. A medium 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, 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 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 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 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 curved forward, and the knees 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 I believe this attitude is 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 was in addition double internal strabismus with retraction of the eyelids, and in another 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 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 soon becomes subnormal. Thus in one experiment, the chart of which I now show you, the rectal temperature, which is usually 100° F. in the 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° F. four days before death.

During the second and third weeks the myxodematous 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 oedema. The appearance of the face is shown clearly in Figs. 3 and 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 twenty-four days, but he showed that when the temperature of the air in the cage was maintained at 90° F., the average duration of life was increased to one hundred and twenty-five 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 myxodema 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 myxodema 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 oedema, dry skin, and loss of hair. In the monkey we have, however, acute nervous symptoms which do not occur in primary myxodema, 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

Fig. 3.—Monkey after thyroidectomy showing attitude and swelling of face.

Fig. 4.—Monkey after thyroidectomy showing swelling of eyelids and lips.

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 versa* 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 due, I believe, to the loss of the parathyroid.

Opportunities for 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 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, whose report proved the identity of the two conditions and their dependence upon loss of function of the thyroid gland.

Fig. 5.—Thyroid gland and hypophysis from a case of myxœdema.

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 secreting 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 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 $1\frac{1}{4}$ in. in length and the left lobe $1\frac{1}{2}$ in., and the isthmus $1\frac{1}{4}$ in. 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 grams, or only about one-tenth of the normal weight. The microscopical structure is

Fig. 6.—Thyroidal fibrosis with advanced atrophy.

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 eighteen 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 grams. 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 could be formed by the gland shown in Fig. 6, and certainly none at all 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 a

recent paper¹² 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, etc. 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.

Fig. 7.—Thyroidal fibrosis with complete atrophy.

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.

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THE GERMAN RED CROSS MEDAL.—A new decoration (the Red Cross Medal) has been created by the German Emperor, at the suggestion of the Empress. The medal, in three classes, will be given to persons belonging to the Red Cross Association who distinguish themselves particularly by their zeal. The medals of the second and third classes will be silver and bronze respectively, bearing on the one face the Red Cross with the letters W. R. (William Rex) on top, and at bottom the letters A. V. (Augusta Victoria). On the other face is the inscription "Für verdienste um das Rothe Kreuz" (for services rendered to the Red Cross), surrounded by a wreath of oak leaves. On the medal of the second class, the cross is of red enamel. The insignia of the first class consists of a cross in red enamel with a silver edge, and gold crowns up the four extremities. The medals of the second and third classes are suspended from a red, black, and white ribbon, while the cross of the first class is worn on the left breast as an order. It is intended to confer this decoration (Die Rothe Kreuz-Medaille), not only on men, but also women and girls who have successfully worked for some years in the interests of the Red Cross, or who have distinguished themselves by remarkable personal acts of devotion in any rank of life.