The Erasmus Wilson lectures on the pathology and diseases of the thyroid gland / by Walter Edmunds.

THE PATHOLOGY AND DISEASES OF THE THYROID GLAND

BY

WALTER EDMUNDS, F.R.C.S.

The Erasmus Wilson Lectures

ON THE

PATHOLOGY AND DISEASES

OF

THE THYROID GLAND

DELIVERED BEFORE THE ROYAL COLLEGE OF SURGEONS OF ENGLAND ON FEBRUARY 18th, 20th, and 22nd, 1901.

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The Erasmus Wilson Lectures

ON

THE PATHOLOGY AND DISEASES OF THE THYROID GLAND.

LECTURE I.

Mr. President and Gentlemen,—The subject of the lectures which the Council has done me the honour to elect me to give is the Pathology and Diseases of the Thyroid Gland. The subject is not new to this theatre, for in 1891 Mr. James Berry selected the pathology, diagnosis, and surgical treatment of goître for the Hunterian lectures which he gave that year, but in the ten years which have since elapsed considerable progress has been made in our knowledge of the physiology of the thyroid gland, and it is therefore convenient to reconsider our views as to the nature of its diseases, and more especially of Graves's disease, in the light of these advances.

The thyroid gland consists mainly of closed vesicles lined with epithelial cells which secrete the colloid; it may here be remarked that the normal vesicles are in shape round or square (in some conditions they become branched and stellate), that the secreting cells are cubical (in some conditions they become columnar), and that the colloid readily stains with the usual microscopic agents (in some conditions it does not so stain). It may be added that the nerves to the thyroid have been traced into close proximity to, but not actually into, the secreting cells. Besides the thyroid proper there are certain small glands named

"parathyroids." Recent researches have shown these to be of much importance in the organism; indeed, their excision generally causes the death of the animal. These glands were

FIG. 1.

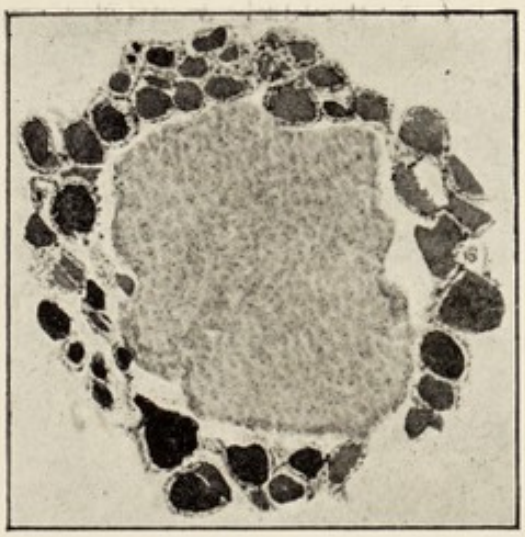
Normal parathyroid gland of the dog. A small part of the adjacent thyroid gland proper is shown and can be recognised by its vesicles containing colloid. In the dog the parathyroid gland lies on the surface of the thyroid gland. (× 50.)

no doubt observed from time to time by various anatomists, but the first full account of them was written by Sandström of Sweden in 1880. In this country they were independently

described by Cresswell Baber in a paper published in the Philosophical Transactions of the Royal Society in 1881. The parathyroid glands differ from the thyroid gland proper in that they consist wholly of cells and contain no vesicles and no colloid, or at most a minute droplet (Fig. 1 and Fig. 2).

It is not easy to identify the parathyroid glands in the human subject because some of the minute outlying nodules are found to consist of ordinary thyroid tissue and to be therefore accessory thyroid glands; only those that consist exclusively or mainly of cells are to be regarded as parathyroid glands. The

FIG. 2.



Normal parathyroid gland of the monkey. The parathyroid gland is completely surrounded by the thyroid gland proper. (× 50.)

anatomy of the parathyroid gland in man has been worked out by Dr. D. A. Welsh of Edinburgh. He finds that there are four of these glands—one anterior and inferior to, one posterior and superior to, each thyroid lobe. The parathyroid glands are said to differ from the thyroid gland proper in another way—developmentally; they develop in advance of the thyroid lobes.

We can study the physiology of the thyroid gland by operations for its removal in whole, in part, or in successive parts; also by the administration of preparations from the thyroid gland or from the parathyroid glands.

The earliest experiments on excision of the thyroid gland were made by Sir Astley Cooper as long ago as 1824.

In 1844 Sir John Simon made an important contribution to the subject. He proceeded by the very Hunterian method of studying the comparative anatomy of the organ, and embodied his results in a monograph on the thyroid gland in vertebrata which was published in the Philosophical Transactions. He came to the conclusion that the thyroid gland is intimately concerned in the nutrition of the central nervous system and in the regulation of the circulation to the brain. It is interesting to note that these views, arrived at more than half a century ago mainly through comparative anatomy, have recently received confirmation from the experimental methods of to-day.

In 1856 and 1857 Schiff made a series of experiments. He showed clearly the fatal results that usually follow the complete excision of the thyroid gland in dogs and cats. But not much attention was paid to the subject till 1882 and 1883, when Reverdin and Kocher respectively reported cases of excision of the goitrous thyroid gland in the human subject which was followed by serious, and in some cases fatal, results. Schiff now repeated his experiments, and he has been followed by numerous observers. The subject, however, has proved rather complicated, as the results apparently differed in different kinds of animals.

Sir Astley Cooper's experiments were made on the dog, and it will be convenient in the first place to consider the now well-established results which follow the complete extirpation of the thyroid gland and the parathyroid glands in the dog. The symptoms commence generally about 48 hours after the operation. One of the first symptoms noticed, probably the first if the animal is closely observed, is a fibrillar twitching of the muscles ; this can be seen, and it can also be distinctly felt by placing the hand on the dog. Within a day or two this is often followed by a severe attack of general convulsions ; the animal lies down—in fact, it cannot stand—as its limbs are in a state of spastic paralysis ; further, its respirations are hurried, rising to 200 a minute or more. Also during the attack its temperature is raised, sometimes as much as several degrees. These attacks last for an hour more or less and completely pass off, so

that the next day the animal appears to be itself again. The convulsive attacks may recur and in a day or two other symptoms may appear ; the dog becomes much less lively—in fact, quite listless. Its hair falls out and a peculiarity is noticed in its gait ; also it has a difficulty in maintaining its equilibrium, especially when turning round. Later a rigidity is noticed in its limbs, and before long its hind legs may become completely paralysed ; trophic symptoms may come on, such as ulcers on the skin, also a conjunctivitis followed by a keratitis leading to destruction of the eye. It may be added that the urine sometimes contains albumin and more rarely sugar ; also that between the convulsive attacks the temperature is subnormal. Finally the animal dies on about the fifth day, but death may occur at any time between the second and the eleventh day, or even later.

There is one other point which, considering its bearing on Graves's disease, ought not to be overlooked, and that is whether there is any alteration in the prominence of the eyes. It is much affected ; the palpebral fissures become narrower and the eyes less prominent.

Although the great majority of the dogs submitted to total thyroidectomy die, a small percentage recover ; this result seems to be common to nearly all observers, and cannot therefore be explained away by error of experiment. We must conclude that even in dogs and cats total excision of the thyroid and parathyroid glands is not necessarily a fatal procedure, and in other less extensive operations be prepared for an absence of absolutely uniform results.

Now, although the operation was followed in dogs and cats with so great a mortality it was found to produce no effect whatever in rabbits. It was soon shown, however, by Gley that the contradiction was only apparent, for he found that two of the parathyroid glands in rabbits lie separate from the thyroid gland proper, and consequently escape removal when the thyroid gland is excised. Gley found that when these were also removed the rabbit, as a rule, died.

In monkeys total excision of the thyroid gland produces symptoms similar to those seen in dogs. The majority of monkeys thus operated on have tremors and convulsions and also

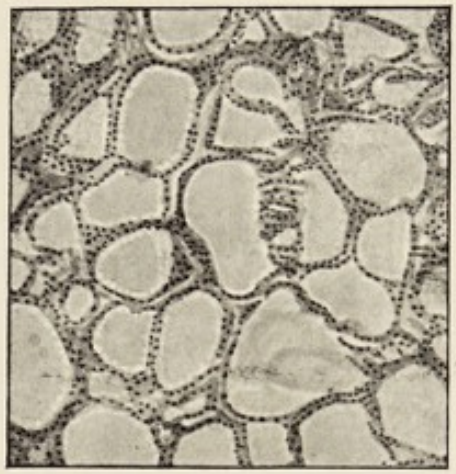
passing paresis of the limbs. They have, too, œdema under the eyelids, and occasionally well-marked swellings there. Finally, the monkeys nearly always die, many with acute nerve symptoms similar to those seen in dogs; others have, as was first pointed out by Horsley, symptoms identical with myxœdema in man. The hair falls out and swelling occurs in the face which is especially marked under the eyelids. In monkeys, too, enophthalmos and narrowing of the palpebral fissures occur, but exceptionally widening of the palpebral fissures may be seen.

The fatal termination in dogs cannot, as a rule, be prevented by thyroid gland feeding or by the subcutaneous injection of thyroid extract. The conclusions which I arrived at from some experiments on this point were that the symptoms were somewhat modified, the attacks of convulsions with rapid breathing being less frequent; that death occurred on an average a few days later than in untreated cases; and that the small percentage of recoveries was somewhat increased. Cunningham came to similar conclusions: he found that by thyroid gland feeding the lives of thyroidless dogs could be prolonged from an average of from 52 to 54 hours to an average of from eight to 12 days. It has been thought that the lives of the animals might be saved by grafting into them the excised thyroid lobes, and with this view a lobe has been returned to the site from which it has just been excised or it has been placed in the abdomen. The result, however, in most cases at least, has been that the grafted lobe has simply been absorbed (that certainly has been the result in my experiments on this point) and the dog has died. This treatment, however, is not absolutely without effect, for during the process of absorption the lobe acts as thyroid gland food and the course of the ailment is slightly modified accordingly. In monkeys, too, thyroid gland feeding, although it modifies and prolongs the course of the disease, fails as a rule to save the life of the animal. Such, then, are the results of total excision.

If in a dog one lobe of the thyroid gland, together with its two parathyroid glands, is excised, leaving the opposite lobe with its two parathyroid glands, no obvious effect is produced on the dog; and if the remaining lobe and its parathyroid glands are subsequently removed the dog dies, and this occurs no

matter what the interval between the two operations may have been; similarly with piecemeal excision, the dog dies after the removal of one of the later pieces.

FIG. 3 AND FIG. 4.



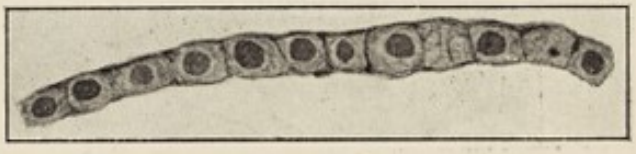
The upper figure shows the normal thyroid gland of the dog. The lower figure shows a portion of the thyroid gland left *in situ* for 41 days after the whole of one lobe and nearly the whole of the other lobe of the thyroid gland had been excised, leaving only one parathyroid gland and a small portion of thyroid gland proper. The vesicles are enlarged and their lining membrane is folded. The colloid has nearly disappeared. The drawings are to the same scale. (× 90).

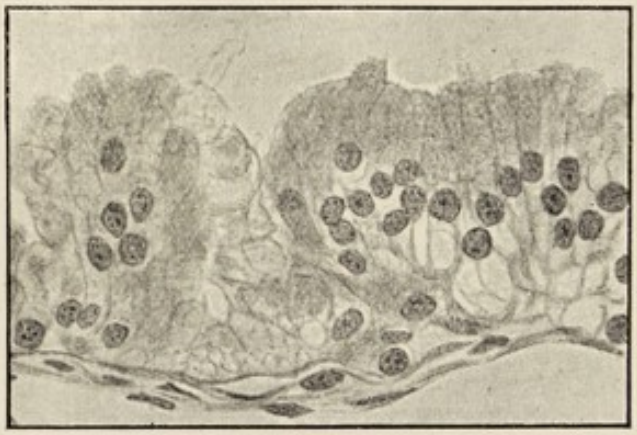
Although no symptoms occur in a dog as a consequence of the removal of one lobe of the thyroid gland important changes occur in the lobe which is left; as was pointed out by Wagner, it hypertrophies. The microscopical changes were first

described by Horsley; the vesicles enlarge and become branched, the cubicle secreting cells become columnar, and the colloid disappears and is replaced by a mucous secretion which takes the staining reagents badly (Fig. 3, Fig. 4, Fig. 5, and Fig. 6).

Whether there is any difference in the physiological action of normal colloid and that of the secretion in compensating hypertrophy we do not yet know, but it is a point worth investigating.

FIG. 5 AND FIG. 6.





The upper figure shows the normal secreting cells lining the vesicles of a dog's thyroid gland. The lower drawing shows the same cells from a small portion of the thyroid gland which had been left together with a parathyroid gland 132 days after the greater portion of the thyroid gland had been excised. The drawings are to the same scale (× 600).

In order to ascertain to what extent the symptoms produced by total excision are due to the excision of the thyroid gland proper and to what extent to excision of the parathyroid glands it is necessary to excise them separately. In dogs if one parathyroid gland be dissected free from the thyroid lobe, taking care not to interfere with its blood-supply, and be left in the animal, and the rest of the thyroid gland on

that side be excised and also the whole of the thyroid gland with its two parathyroid glands on the opposite side, so that only one parathyroid gland be left in the animal, the dog will live and no obvious effects will ensue ; such, at least, is the usual result. If the parathyroid gland is subsequently excised the dog will die with the usual acute symptoms. The parathyroid glands that are left in these experiments show signs of more active growth than the normal, but they do not develop into thyroid tissue proper. No vesicles form. This, it will be noticed, tells against the view that was once held, that the parathyroid glands are undeveloped thyroid tissue.

In rabbits the excision of the thyroid lobes with the two attached parathyroid glands, leaving *in situ* the two other parathyroid glands, produces, as already stated, no immediate effect ; but if the animals are kept for several months the following symptoms may arise. In four experiments I noticed (1) failure of health, (2) hair falling out, and (3) a swelling of the lower part of the face, presumably myxœdematous in nature. Dr. G. R. Murray of Newcastle has also observed myxœdematous changes coming on late in rabbits which have been deprived of their thyroid glands proper. With respect to the condition of the eyes in these animals which have been deprived of their thyroid glands proper, in dogs I have not noticed, as a rule, any change ; but in one dog still under observation there have recently come on symptoms—tremors and spastic gait—and for months past it has been noticed that the eyes have appeared sunken and the palpebral fissures narrower ; these symptoms are getting worse. In rabbits a series of experiments were made especially to test this point, the result was that there was found a marked tendency for the eyes to become narrow ; if eventually the animals died from thyroid symptoms the eyes became very narrow.

LECTURE II.

Mr. President and Gentlemen,—Having in the previous lecture considered the effects produced by total excision of both the thyroid gland proper and the parathyroid glands, and also by the removal of the thyroid gland only, we have now to determine the results of removing the parathyroid glands only.

In 1896 it was pointed out by Vassale and Generali that if in dogs all the parathyroid glands were removed and the thyroid gland proper left the dogs would die just as they do, and with the same symptoms, as when the thyroid gland and the parathyroid glands are completely removed. Their experiments have now been repeated several times, and in the main they have been confirmed. My own results were as follows. In 16 dogs it was intended to remove all four parathyroid glands, leaving the thyroid lobes intact; but it is not easy to find all the parathyroid glands in an operation, and it was subsequently seen that in seven of the dogs one (and in one case two) of the parathyroid glands had been left; in only nine then had all the parathyroid glands been removed, and it cannot be absolutely affirmed that in these no parathyroid had been left, because the only way of making sure is to cut and to examine consecutive sections of both thyroid lobes, and this was not done. However, in the nine dogs no parathyroid glands were subsequently found, and it is probable that none were left. Of the nine dogs four died; one in two days, one in four days, one in seven days, and one in 28 days. The other five survived, but three of them had temporary symptoms; thus, of the nine dogs which underwent complete parathyroidectomy four died, three recovered after symptoms, and two escaped all ill consequences. In my hands, therefore, the results of parathyroidectomy were not so bad as were those of total excision, but, on the other hand,

in a recent paper Vassale and Generali state that they have found them even worse—that is to say, that while both operations are fatal the dogs die more quickly after removal of the parathyroid glands only than after total excision, and further, that if after parathyroidectomy the thyroid lobes are removed a day or two later the dogs will live longer than they would have done had the lobes been left.

The changes which occur in the thyroid lobes which are left in these operations are very interesting—the colloid diminishes or completely disappears, and its place is taken by a watery secretion ; the vesicles instead of remaining round become branched and the secreting cells become columnar or multiplying fill the cavity of the vesicles with round cells. These changes are identical with those described as "compensatory hypertrophy," but the thyroid lobes do not appear to enlarge, but on the contrary sometimes they seem to become smaller ; this, if confirmed, will coincide with the view that the parathyroid glands manufacture the secretion and the thyroid glands store it ; when the parathyroid glands had been removed there would be no secretion for the thyroid lobes to store. The five dogs which, as just stated, survived excision of the parathyroids were subjected to the further operation of removal of one of the remaining thyroid lobes ; two died after this and three survived ; in these three the remaining thyroid lobe was excised ; one died, and two, after temporary symptoms, recovered ; these two lived therefore without either thyroid gland or parathyroid gland —in a state of complete athyroidea, in fact. The symptoms, and in the fatal cases the cause of death, were the usual symptoms of athyroidea—namely, tremors, unstable gait passing into paralysis of the hind limbs, emaciation, and great weakness ; in two of the dogs marked narrowing of the palpebral fissures was noted. The thyroid lobes obtained by these later operations were sometimes normal and sometimes altered as described. In seven of the dogs some of the parathyroid glands had been removed, but it was subsequently found that in them one (and in one case two) of the parathyroid glands had been left. Only one of these dogs died, and that only after 72 days ; thus in nine dogs with complete parathyroidectomy four died in 28 days ; in seven dogs with incomplete parathyroidectomy only

one died, and that only after 72 days ; it died with paralytic symptoms. Although the other six dogs did not die, four of them had symptoms from which they recovered ; these six dogs were submitted to further operations ; in one both thyroid lobes were removed simultaneously ; it died in consequence ; in the other five one thyroid lobe was removed ; three died in consequence ; two survived, but one of them had symptoms ; from each of these two survivors the remaining lobe was removed ; they both died in consequence. Changes were noticed in the eyes of some of these dogs ; in two of the dogs after an incomplete excision of the parathyroid glands widening of the eyes was seen and after a later operation the eyes became retracted and the palpebral fissures narrowed. In one dog two parathyroid glands were removed and two left, one on each side ; this operation produced no change in the eyes ; the removal of one parathyroid gland with one lobe was followed by widening of the eyes, and the subsequent removal of the other lobe, also with a parathyroid gland, was followed by narrowing of the eyes and death from athyroidea. It would seem that removal of the parathyroid glands, if not fatal, causes (if any change) exophthalmos, but in fatal cases, whether produced by the removal of the parathyroid glands or by total thyroidectomy, the eyes often become very narrow.

We have now completed our survey of the effects of the three main excision operations, but on account of the importance of exophthalmos in Graves's disease it will be well to review the effects of these operations on the eyes.

To commence with dogs. The effects on the eyes of dogs of complete excision of both the thyroid gland and the parathyroid glands is to make the eyes narrow ; the dogs die from the operation and with narrow eyes. The next operation is removal of one lobe of the thyroid gland together with its two parathyroid glands, leaving the opposite lobe with its two parathyroid glands ; this produces no effect on the health of the dogs, nor, as far as I have noticed, on their eyes. The same result, as a rule, follows removal of the thyroid gland proper, leaving one or more parathyroid glands. Occasionally after leaving only one parathyroid gland symptoms come on, and then the eyes may become narrow. Removal of parathyroid glands, leaving one parathyroid

gland and the whole or part of the thyroid gland proper, may be followed by the eyes becoming wide, and after a further operation they may become narrow. Finally, total excision of all of the parathyroid glands often causes death, and in one case at least there was narrowing of the eyes.

In rabbits two of the parathyroid glands lie distinct from the thyroid gland as a rule, and it is a simple operation to remove these and to leave the thyroid gland proper with presumably two parathyroids, or to perform the reverse operation. I made a series of experiments to test the effects of these operations on the eyes. Of six rabbits in which the thyroid gland was removed three have since died, and they died with narrow eyes; in one of the survivors the eyes are now normal, having once been narrower than before operation; in one they are now normal, having once been wider; and in the third they are becoming normal, having been wider. On the other hand, a much stronger tendency to the eyes becoming wide was seen in the rabbits from which two parathyroid glands were removed; out of five experiments in one no change occurred, but in all the other four the eyes became wide for a time, but have since become normal.

In monkeys the only operation performed was total excision of the thyroid gland and the parathyroid glands; as a rule (and always at the latter stage of the illness when the monkey is dying from athyroidea) the eyes are narrower; but occasionally after the operation the eyes become wider.

The conclusion of the matter would seem to be that excision of the thyroid gland and the parathyroid glands produces enophthalmos with narrowing of the palpebral fissures; total parathyroidectomy would seem to produce the same, and so also (if it produces symptoms) does excision of the thyroid gland proper, but certain operations not fatal at the time, and especially those in which the parathyroids are interfered with, may be followed by exophthalmos with widening of the palpebral fissures. The same operation may be followed by first widening and later narrowing, but I have never seen the reverse—at least, not as a permanency. It will be noticed that these eye changes tend to support the suspicion that the parathyroid glands are involved in the pathology of Graves's disease.

The preceding experiments apply to the action of the thyroid gland, or of portions of it, when the nervous supply is intact ; but the well-known effect on the salivary glands of interference with their innervation leads to the question whether the internal secretion of the thyroid gland is under the control of the nervous system. Various experiments have been made to test this: Schiff stripped the sympathetic fibres accompanying the blood-vessels going to one lobe of the thyroid gland from them, leaving the opposite lobe intact; on subsequently comparing the lobes of the two sides he could find no difference between them; the interference with the sympathetic had produced no result. Horsley tried the effect of dividing the recurrent laryngeal nerve to one lobe; that, too, produced no difference on the two sides. I myself divided the vagus on one side; as the division was below the origin of the superior laryngeal nerve the operation was practically the same as Horsley's division of the recurrent laryngeal nerve and the result was the same—a negative one. Katzenstein tried the effect of electrically stimulating one lobe of the thyroid gland; that, too, produced no alteration in the microscopical appearances of the two sides. However, at last a positive result was obtained. Exner found in two experiments on cats that the division of the superior and inferior laryngeal nerves supplying one lobe of the thyroid gland and the excision of the opposite lobe caused severe tetany, showing that the function of the "paralysed" lobe was greatly interfered with. I have repeated Exner's experiment (with an unimportant modification) and have obtained similar results. The experiments were made on dogs and consisted in excising a length of the superior laryngeal nerve on one side and also on that side a length of the vago-sympathetic at the level of the thyroid, and finally on the opposite side excising the thyroid lobe together with its parathyroid gland. The experiment was performed nine times; the result was that three of the dogs died, one in 18 hours, one in two days, and one in three days. Of the six survivors four had athyroidic symptoms and two had no symptoms; thus out of nine dogs operated on seven had symptoms and three of them died; it is therefore to be inferred that the secretion of the thyroid gland is under the control of the central nervous system; that this is so is further supported by the

microscopical examination of the thyroid lobes which had had their innervation interfered with. Out of the nine experiments two dogs survived without symptoms; in one the first lobe removed did not appear normal under the microscope and it will therefore be safer to reject this experiment altogether; in one the operated lobe appeared normal; as this dog had no symptoms it is possible that there was something wrong in the experiment—any way, the absence of symptoms and of alteration in the lobe go well together. With respect to the remaining dogs which had symptoms, from two there are no specimens,

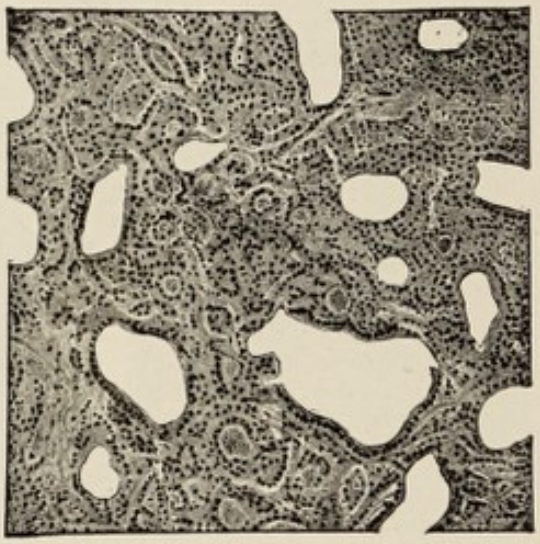
Fig. 7.

From a dog the parathyroid glands were removed; the dog died in seven days in consequence. The drawing shows the changes which occurred in the thyroid lobes (which were left).

from one because the dog is still alive; there remained then five specimens from five dogs, all of which had symptoms. The results of microscopical examination were: (1) from all five of these lobes the colloid had completely disappeared; and (2) in four of them the secreting cells had multiplied into the cavity of the vesicles; this is different from the usual appearances in compensating hypertrophy, in which, as a rule, the secreting cells become columnar but do not invade the cavity of the vesicle—it is rather the appearance seen in any remaining portion of a lobe when compensation has failed and death is occurring from athyroidea (Fig. 7). With respect to the fifth

lobe, the dog having survived the experiment the lobe was excised 49 days later. It was greatly enlarged, and weighed 3.5 grammes, which is three or four times the normal weight. All colloid had disappeared, but the secreting cells and their progeny were not in this case filling the cavities of the vesicles which contained instead a watery secretion. The great size of the lobe was due to the growth of young thyroid tissue between the vesicles (Fig. 8). It is clear then that the interference with the nerve-supply produces very serious symptoms, and when we come to consider the pathology of thyroid disease we must be

Fig. 8.



A microscopical section of the thyroid lobe of the dog referred to in the text.

prepared to admit the possibility of defective innervation being the cause of serious symptoms and pathological changes. With respect to the sympathetic nerve-supply, Schiff, as stated, came to the conclusion that it produced no effect. In the submaxillary gland the sympathetic carries but few secreting fibres, the main supply being through the chorda tympani. Such, then, are the results of deprivation of thyroid secretion by operations for the removal of the thyroid system in whole or in part, or by interference with its nerve-supply.

We now proceed to consider the results arising from an excess of thyroid gland in the system. This can theoretically

be effected in two ways—either by grafting additional thyroid gland into the body or by the administration of thyroid gland for thyroid preparations. Grafting, as already stated, seems unsatisfactory, and it has not yet been carried out so as to justify any physiological conclusions as to its effects; on the other hand, the results of thyroid-gland feeding have been carefully investigated both in normal and in diseased subjects. In a healthy man Dr. G. F. Johnston found by experiments on himself that after taking from four to nine thyroid-gland tablets a day there was acceleration of the pulse from 70 to 120, accompanied by palpitation, flushing, tremors, sensation of heat, and perspirations. Similarly, M. Gagnevin, a medical student, took for eight days full doses of raw thyroid gland; this produced palpitation, a rapid pulse, tremors, perspiration, flushings, and (as was noticed by his friends) exophthalmos. Also Dr. Béclère has recorded a case of myxœdema in which very large doses of thyroid-gland preparation were taken. The disease was relieved, but temporary symptoms of thyroid intoxication were produced; they were quickened pulse, quickened respiration, rise of temperature, sensations of heat, increased perspiration, mental agitation, tremors, incomplete paraplegia, increased secretion of urine, temporary albuminuria, and a certain degree of exophthalmos. Similarly, Easterbrook found in the human subject that the administration of thyroid gland produced: (1) a loss of weight, about seven pounds a week; (2) some pyrexia; (3) some increase of perspiration; (4) diminution of red blood corpuscles; (5) headache; (6) tremors; (7) an increase of pulse-rate by about 40 a minute; (8) an increase of rate of perspiration by about six a minute; (9) a diminution of appetite; (10) an increase of menstruation; and (11) an increased amount of urine, often albumin, but never sugar. He concludes that thyroid substance is a profound katabolic stimulant.

In healthy animals thyroid-gland administration does not produce much effect unless carried out in very large doses. I gave a dog two thyroid glands of the sheep a day without any obvious effect, also to another dog the thyroid glands of 16 sheep without any result, and others have made the same experiment also with negative results. Chasevaut fed a dog

with the thyroid gland of the ox. He gave to the dog in 57 days 1361 grammes of thyroid gland; the only result was loss of flesh—the weight fell from six and a half to eight kilogrammes; there were no other symptoms, no rise of temperature, no loss of good temper, and no morbid symptoms whatever. In 1895 Ballet and Enriquet experimented on dogs in three ways: by thyroid-gland grafts in two cases, by thyroid feeding in six cases, and by thyroid injections in 12 cases; in three out of the six dogs fed with thyroid gland distinctive symptoms were obtained; these consisted in rise of temperature, rapid pulse, tremors, conjunctivitis, emaciation, and in one animal quite distinct exophthalmos. In two of the animals in which the injections were used there was observed to be a slight prominence of the eyes not amounting to exophthalmos.

In a rabbit to which Cunningham administered by the mouth 0·1 gramme of thyroid extract exophthalmos was caused. He gives a photograph of the rabbit which shows the exophthalmos very clearly.

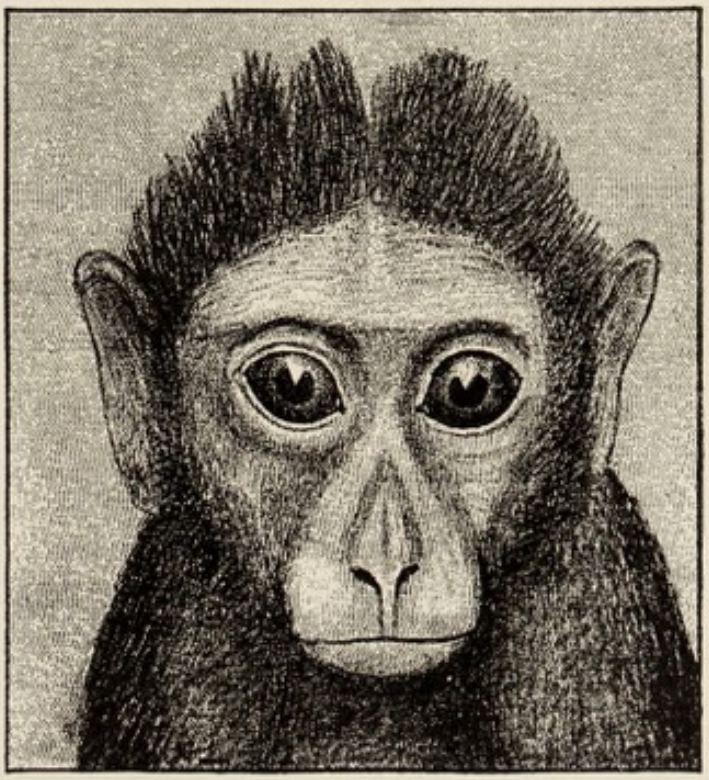
In monkeys I have found the administration of large doses of thyroid extract produce marked results. The preparation chiefly used was thyro-colloid which is made from the thyroid glands of sheep by a process devised by Dr. R. Hutchison. In principle it consists in dissolving out the colloid with a dilute alkaline solution and precipitating with acetic acid. Large doses of this preparation were administered to six monkeys, the daily dose corresponding to from one-half to three whole thyroid glands of a sheep a day. Well-marked symptoms were produced —namely, proptosis, dilatation of pupils, widening of palpebral fissures, erection of hairs on the head, the hair falling out in patches, paralysis of one or more limbs, emaciation and muscular weakness, and finally death from asthenia. The average life of the monkeys after the commencement of this treatment was 76 days (Fig. 9 and 10).

Of the above effects those produced on the eyes are no doubt caused mainly by action through the cervical sympathetic. Division of the cervical sympathetic causes (1) recession of the eyeball, (2) contraction of the pupil, (3) narrowing of the palpebral fissure, (4) œdema and flushing of the skin round the eye,

FIG 9

Monkey before treatment.

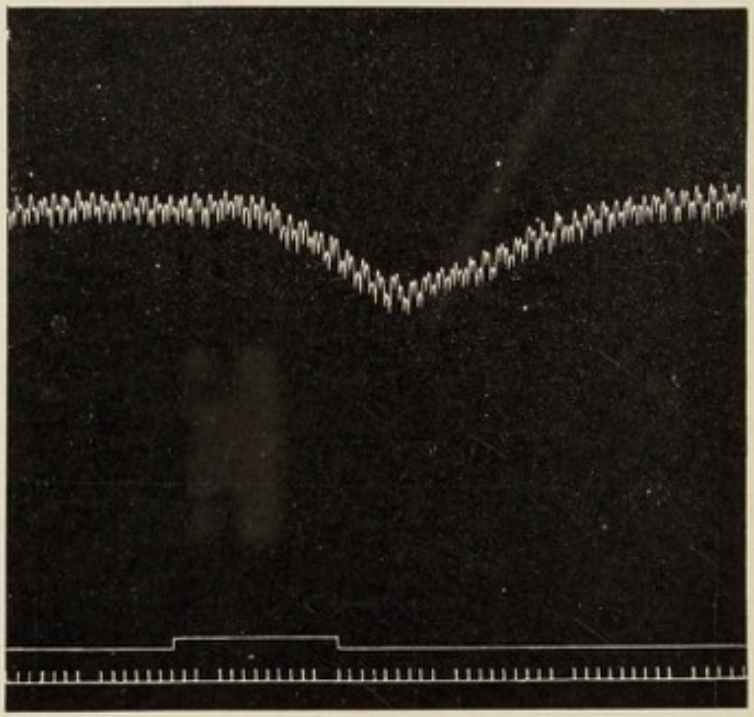
FIG. 10



Same Monkey after nine weeks' treatment by thyroid feeding: the eyes are prominent, the palpebral fissures widened, and the hair on the head is standing on end.

(5) swelling of the caruncle, (6) projection of the pinna from the side of the head, (7) puckering of the skin of the muzzle, and (8) flattening of certain hairs on the forehead which cannot then be elevated by emotions which affect the corresponding hairs on the opposite side. On the other hand, stimulation of the cervical sympathetic produces : (1) proptosis of the eyeball ; (2) well-marked dilatation of the pupil ; (3) widening of the

FIG. 11.



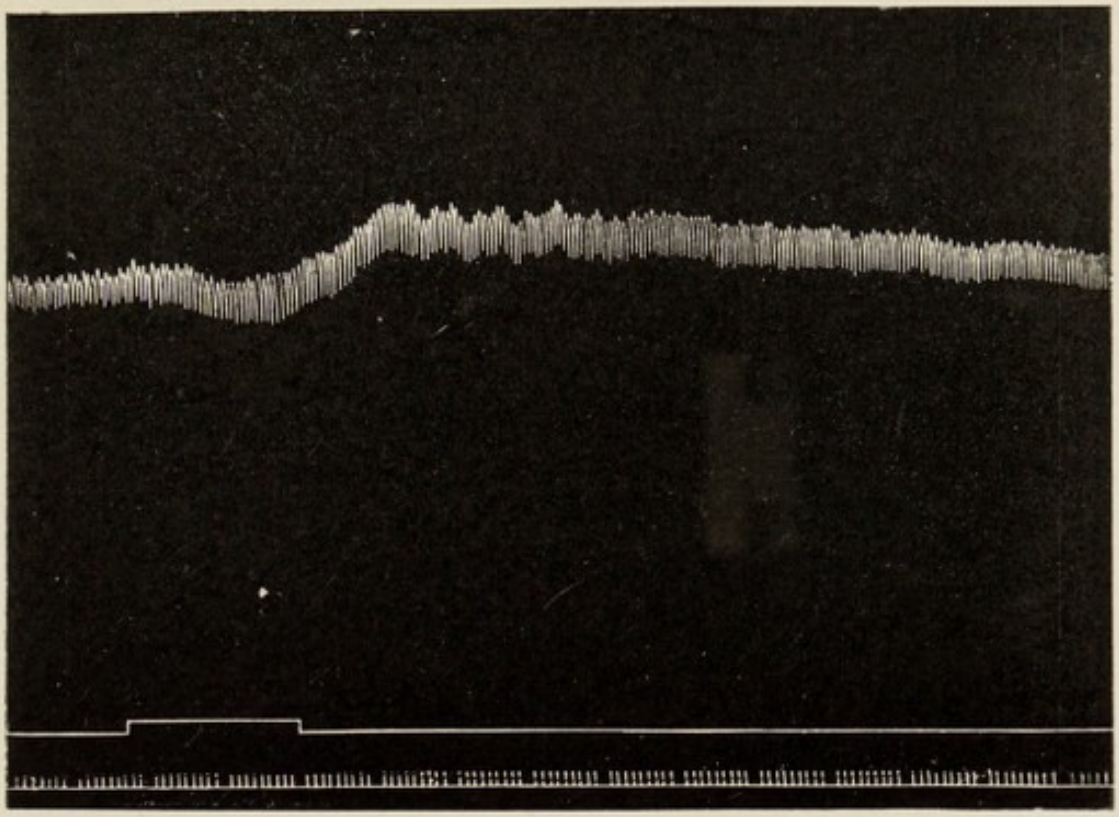
The effect of intravenous injection of thyroid extract into the normal dog. The injection was made during the time shown upon the upper line; it caused a fall in blood-pressure. (Read the tracings from left to right.)

palpebral fissure ; (4) lying back of the pinna ; and (5) erection of certain hairs on the head.

In order to test how far the effects upon the eye of thyroid-gland feeding were produced through the sympathetic in two monkeys I excised a length of the cervical sympathetic on one side. After allowing a few days for recovery from the effects of the operation thyroid-gland feeding in large doses was commenced; 12 days later it was found on comparing the monkeys with

sketches made before operation that on the unoperated side the palpebral fissure had become very wide, the eyeball very prominent, and the pupil much dilated. On the side on which the sympathetic had been divided the fissure was narrow, the eyeball not prominent, and the pupil not dilated. In one of the monkeys 12 days later the difference in the eyes was much less marked, although the feeding had been continued; this may

Fig. 12.



The effect of the earlier intravenous injections of thyroid extract into a dog suffering from experimental athyroidea; it causes a rise in the blood-pressure.

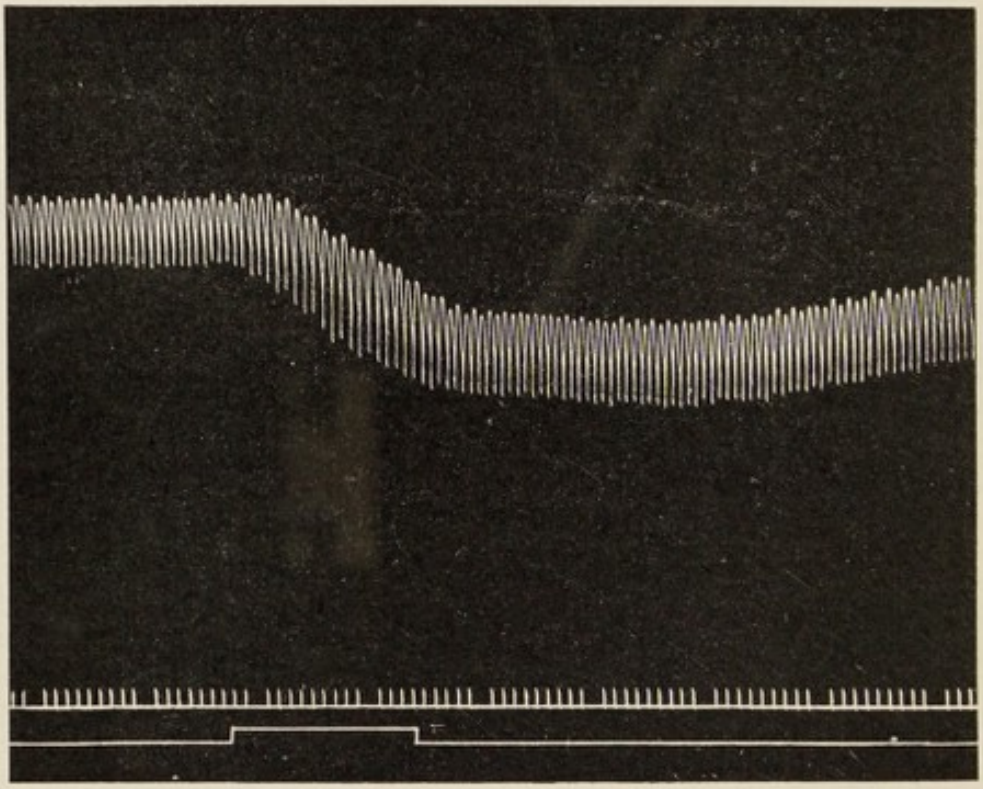
possibly be due to some repair having occurred in the sympathetic. This is said to happen even when, as in this case, a length of the nerve has been excised.

There are comparatively few observations on the action of parathyroid gland. Easterbrook in his investigation found that it produced no effects, thus markedly contrasting with the thyroid gland. Hutchison tried parathyroid gland in a case of

myxœdema, but without producing any improvement; but Hutchison states that parathyroid gland undoubtedly produces beneficial results in animals that have been deprived of their parathyroid glands.

The effect of the intravenous injection of thyroid extract into animals has been investigated by Oliver and Schäfer; they found a marked fall in the blood-pressure produced, but the force of

Fig. 13.



The effect of the later injections of thyroid extract into a thyroidless dog; it causes, as in the normal, a fall of blood-pressure.

the heart's contraction and the pulse-rate were not materially altered.

The effects of the injection of thyroid extracts into thyroidless animals have been tried by von Cyon who has written a series of very interesting papers on the relations of the thyroid gland and the heart, and (with the kind assistance of Dr. T. G. Brodie) by myself. The injection of thyro-colloid into thyroidless dogs causes a rise of blood-pressure—at least, that is the effect of the

earlier injections ; later injections produce, as in the normal, a fall ; these phenomena may be explained by assuming that thyro-colloid stimulates both the depressor and accelerator mechanisms, that while the former preponderate in the normal, athyroidea so alters their relative response that in it the accelerators preponderate at first, but that the earlier injections of thyro-colloid so revives the depressors and vagi that the later injections produce the normal effect. Von Cyon states that in the goitrous animals of Berne and in athyroidea the excitability of the vagi and depressors is diminished or abolished and that of the sympathetics (vaso-constrictor and accelerator) is increased. (Fig. 11, Fig. 12, and Fig. 13.)

LECTURE III.

Mr. President and Gentlemen,—With respect to myxœdema and cretinism, as time is short, it must suffice to say here that the working out of the nature and treatment of these diseases is one of the most brilliant of the recent advances of medicine, and that our knowledge of their pathology seems now so well established as to admit of little discussion and to justify us in treating it as firm ground from which to proceed to the investigation of other and probably more complex ailments. But there is one point in connexion with myxœdema which may detain us a minute as it has led to some diversity of opinion. We have seen that in experimental removal of the thyroid gland (whether the parathyroid glands are also removed or not) there is often a narrowing of the palpebral fissures; in myxœdema the palpebral fissures are also narrowed, but the narrowing is generally attributed to the swollen condition of the eyelids. It is, however, doubtful if this is the whole explanation, and, indeed, Allen Starr says distinctly that it is not. "In myxœdema," he writes, "there is a marked tendency to abnormal heaviness of the eyelids, so that the upper lid falls and the eyes are never widely open. This falling of the lid appears to be independent of its thickening by the myxœdema; there is also a retraction of the eyeball. I have noticed in all my cases after a cure of the myxœdema that the eyeball had been previously decidedly retracted, so that when the patient was cured and the eyeball was in its natural position the previous retraction, as shown by photographs, became noticeable."

For cases of sporadic goitre without symptoms—that is to say, cases in which the presence of the goitre is the only trouble—it seems now to be clearly established that the

administration of thyroid gland is the best treatment. I had under my care a case of ordinary goitre in a young girl which was treated with some success with iron, iodide of potassium, and other remedies, but it was not until thyroid gland was administered that rapid improvement took place. Some time after the cessation of treatment a little enlargement of the thyroid gland reappeared, but this again was speedily removed by thyroid gland treatment. A second case of goitre was also cured, at least for a time, by thyroid gland administration. The effects of this treatment are so good that it must be regarded as a specific remedy; if it is, the enlargement of the thyroid gland must, in part at least, be attributed to an attempt at compensation, and that attempt must be unsuccessful, for otherwise the increase in size would not proceed to the large dimensions that it does.

Formerly goitres were occasionally treated by excision, but the constitutional results following this operation were often so serious that complete excision is now abandoned. These results were: (1) a feeling of weakness and lassitude; (2) coldness of the hands and feet even in summer; (3) slowness of thought, of speech, and of other movements; (4) œdema of the eyelids, lips, hands, and feet; (5) bulkiness of the face, hands, feet, and trunk; (6) dryness of the skin and the falling out of the hair; and (7) in children an arrest of bodily and mental development. These symptoms were almost always chronic in their character, and their resemblance to the effects of experimental excision of the thyroid gland proper is noteworthy; but one case of acute myxœdema is on record. From a girl, aged 18 years, the late Sir William Stokes excised one lobe of a large goitre; the only result was a satisfactory diminution of the remaining lobe. After three and a half months the remaining lobe was excised; this after 11 days was followed by convulsive seizures, puffiness of the eyelids, the face, the hands, and the feet, mental torpidity, and slowness of speech. The patient died from exhaustion 21 days after the second operation. The absence of ill-effects after the first operation and the rapidly fatal termination after the second resembles what happens in dogs after the removal of the thyroid gland and the parathyroid glands first on one side and later on the other. Although in goitre the removal of the

whole thyroid gland is now not practised the removal of one lobe is not unusual, both in ordinary goitre and in Graves's disease; this, as in Sir William Stokes's case, is often followed by shrinking of the opposite enlarged lobe. When a goitre causes dyspnœa by pressing on the trachea it becomes necessary to remove a portion, and generally the isthmus is excised; this operation, too, is often followed by atrophy of the enlarged lateral lobes. It is necessary to remember in connexion with pressure symptoms that attacks of dyspnœa occur in Graves's disease, and also, it is said, in ordinary goitre, quite apart from any mechanical cause; they are similar to, and presumably due to the same cause as, the attacks of rapid breathing which constitute so prominent a symptom in the experimental aparathyroidea of dogs.

It is probably best to include under the term "Graves's disease" all cases of goitre with symptoms not to be explained by pressure. No dividing line can be drawn between the typical cases and those with less pronounced constitutional symptoms.

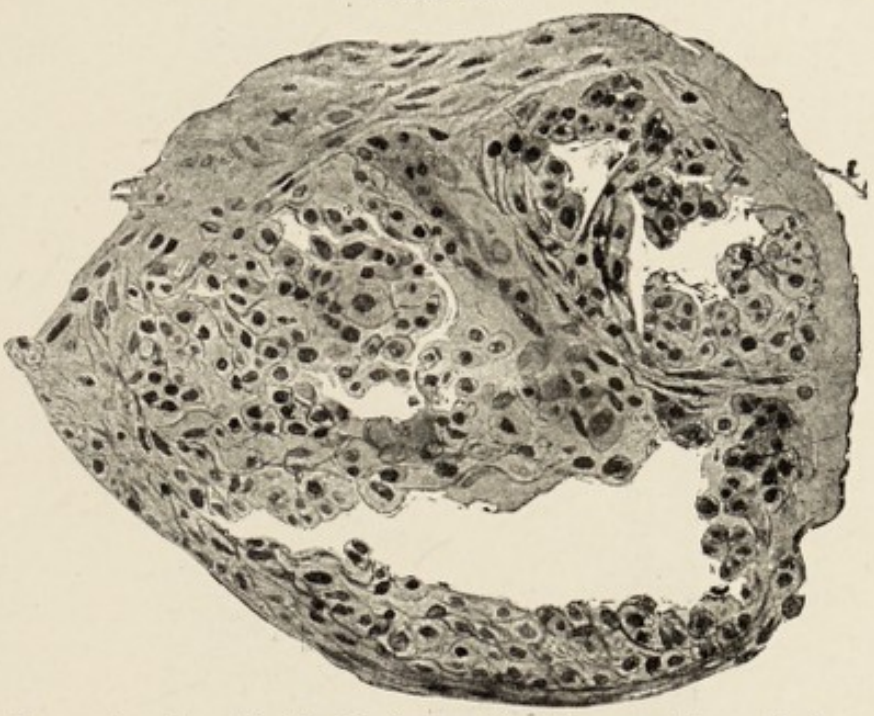
With respect to the pathology of Graves's disease it has been discussed whether the primary lesion is in the nervous system or in the thyroid gland; whether, in other words, some nervous derangement causes the goitre and other symptoms or whether the goitre is the cause of the exophthalmous and cardiac disturbance. Originally the starting point of the disease was thought to be the cervical sympathetic, but latterly it has been contended that the secretion from the goitre is the cause of the palpitation, the exophthalmos and the other symptoms. This view has been urged by Möbius in Germany and in this country by Professor Greenfield, in the Bradshaw Lecture of 1893. There is much to be said in its favour. In the first place, in an ordinary case of Graves's disease the enlargement of the thyroid gland is, as a rule, obvious, and when the opportunity offers it may be seen under the microscope that the gland is in a state of active secretion. On the other hand, the nerve lesions are extremely uncertain; one observer has found one change, one another, and when in a fatal case of Graves's disease a systematic examination of the nervous system has been made the result has

generally been negative. Secondly, the marked contrast that exists between myxœdema and Graves's disease supports the thyroid secretion view. The first, at least in this country, to emphasise these distinctions was Byrom Bramwell and they are well set forth in his recent work. 1. In myxœdema the thyroid gland is atrophied and its secreting structure is destroyed; in Graves's disease the thyroid gland is enlarged and its secreting structure, though modified in character, is increased in quantity. 2. The symptoms of myxœdema almost always come on slowly and insidiously; those of Graves's disease not infrequently come with considerable rapidity, sometimes, indeed, after profound emotion, suddenly. 3. Myxœdema is usually developed at a later age than is Graves's disease; it arises, as a rule, between 35 and 45 years of age, while Graves's disease appears between the ages of 15 and 35 years, very rarely after 50 years of age. 4. In myxœdema the temperature is subnormal; in Graves's disease it is usually normal, but temporary elevations occasionally occur, its equilibrium being easily disturbed, and the patients often complain of feelings of heat and cold. 5. In myxœdema the skin is extremely dry and harsh and perspiration is diminished; in Graves's disease the skin is moist and perspiration is increased. 6. In myxœdema the bowels are usually constipated, whereas in Graves's disease diarrhœa is not uncommon. 7. In myxœdema the mental condition is placid and slow, while in Graves's disease there is considerable mental excitement. 8. Myxœdema is much benefited by thyroid gland treatment; Graves's disease is not, as a rule, benefited by this treatment, and some cases are made worse by it. A third argument in favour of the thyroid secretion view is that, as we have already seen, most of the symptoms of Graves's disease other than the goitre can be produced by the administration of thyroid preparations. A fourth argument is found in the cases of ordinary goitre which after years become converted into cases of Graves's disease; it seems more probable that some change should have occurred in the thyroid gland or secondarily to it than that a primarily central nervous lesion should have produced no other symptoms for years. Graves's disease is not known to occur secondarily to myxœdema. A fifth argument is derived from the good effects which often follow the removal of a portion of the

goitre in Graves's disease. In a considerable number of these cases the removal of a lobe of the enlarged thyroid gland has been followed by marked improvement and, indeed, by cure. But there are certain objections to the secretion view. There seems no doubt that the thyroid gland is always enlarged in Graves's disease and that it is in a state of active secretion, but it does not follow that its secretion is identical with that in health, and although the observations of Hutchison and Soupault tend to show that it is, too much stress must not be laid on arguments derived from the action of normal colloid. In the thyroid gland in Graves's disease there is proportionately less colloid and in some cases no colloid at all. The microscopical examination of the thyroid gland in Graves's disease reveals various changes: (1) the vesicles instead of being round or square in section become branched and stellate; (2) the lining membrane is folded on itself; (3) the secreting cells instead of being cubical are columnar; and (4) the colloid in the vesicles has partly or wholly disappeared and its place is taken by a secretion which takes the microscopic stains badly. Now these changes are practically identical with those of compensatory hypertrophy as seen in animals after partial removal experiments. Indeed, the resemblance is so close as to lead to the conclusion that the changes in the thyroid gland of Graves's disease are also compensatory in character—in other words, that they are secondary to some defect elsewhere in the system; that defect may possibly be in the parathyroid glands, but there is no evidence on that point either way at present. In my experiments of excising the parathyroid glands the thyroid lobes underwent these changes microscopically, but to the naked eye they did not seem enlarged; on the contrary, some of them appeared to be smaller (Figs. 14 to 24). It must be admitted that occasionally in cases of goitre without Graves's symptoms similar appearances are seen, but, as far as my experience goes, this is exceptional. Also against this view may be shown sections from two cases of adenoma of the thyroid gland; in one the sections are like normal thyroid gland and in the other there are hypertrophic changes. The first case had no constitutional symptoms; the second was a case of Graves's disease.

The treatment of Graves's disease has been carried out on various lines. The most obvious treatment is rest. This no doubt benefits the disease, or at least reduces the symptoms, but it is doubtful how far the benefit persists after the patients are up and about again, and unless they are equal to resuming their natural occupations they cannot be said to be cured or even to be nearly cured. Change of air and quietude are also obviously indicated. With respect to the administration of medicines various drugs have been tried. Belladonna stands in

Fig. 14.

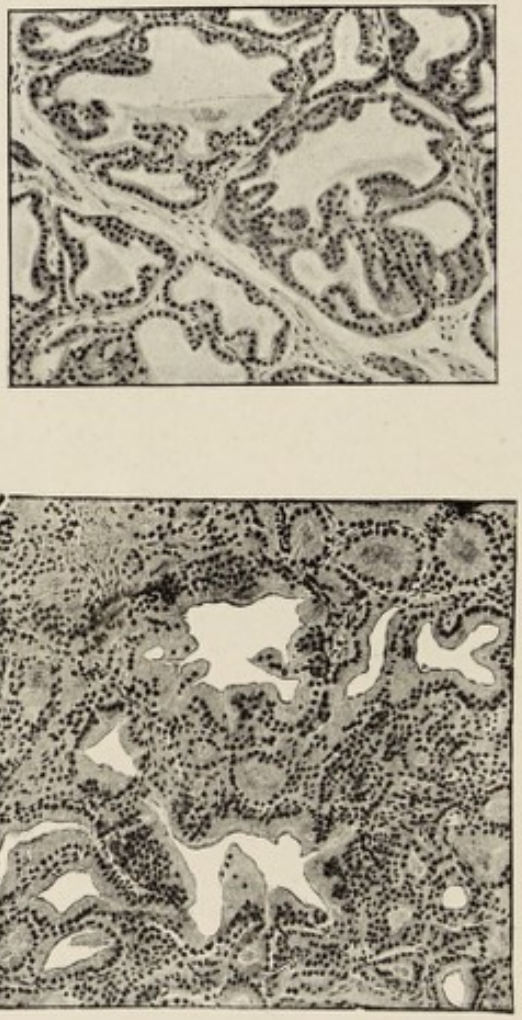


From the thyroid gland of a cretin: the secreting cells have multiplied and are filling the vesicles. (× 250.)

good repute ; it may be supposed to diminish the internal secretion, but its reputation is far older than our modern ideas about internal secretion. Bromide of potassium is also given to quiet the nervous system, valerian has been prescribed with the same idea. In order to reduce the size of the goitre iodine has been used both internally and externally. For their action on the heart digitalis and strophanthus have been given, also as tonics quinine and iron. The administration of thyroid gland preparations has been tried and has given different results in different

cases ; as a rule in doses which would benefit myxœdema no marked results have ensued. In some cases it has been attended with benefit, while on the other hand it has undoubtedly made some patients worse. This was clearly so in a

FIG. 15 AND FIG. 16.

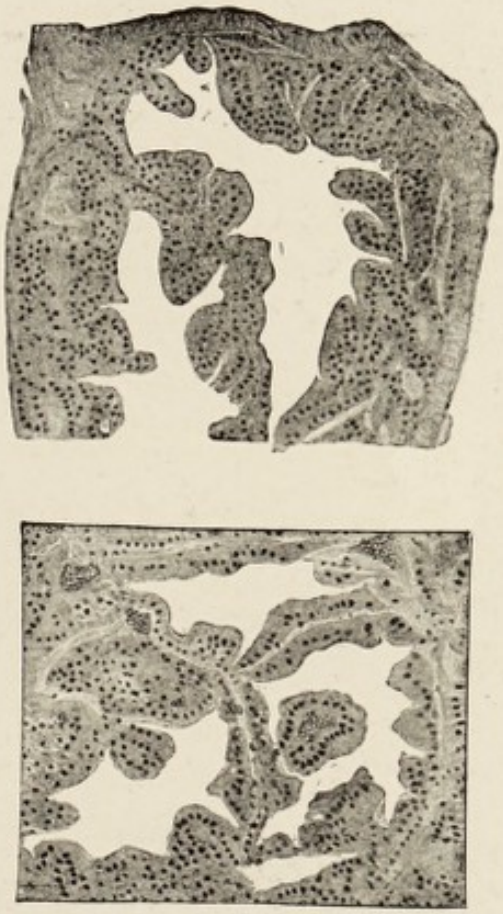


The upper figure shows compensatory hypertrophy in the thyroid gland of a dog 41 days after partial excision of the gland. The lower figure shows the thyroid gland from a case of Graves's disease. (× 90.)

case recorded by Auld in which the exophthalmos was increased, the pulse-rate was raised from 99 to 138, the temperature was elevated above the normal, and diarrhœa, sickness, and vomiting were brought on. Thymus gland feeding has been recommended,

but it often fails to be of any use. Pregnancy, when it occurs, is stated by Charcot to be of marked benefit in Graves's disease ; he mentions two cases and cites in support the high authority of Trousseau. But Graves's disease sometimes arises during pregnancy. Myxœdema is also said to be benefited by pregnancy, the explanation given being that the mother shares

FIG. 17 AND FIG. 18.

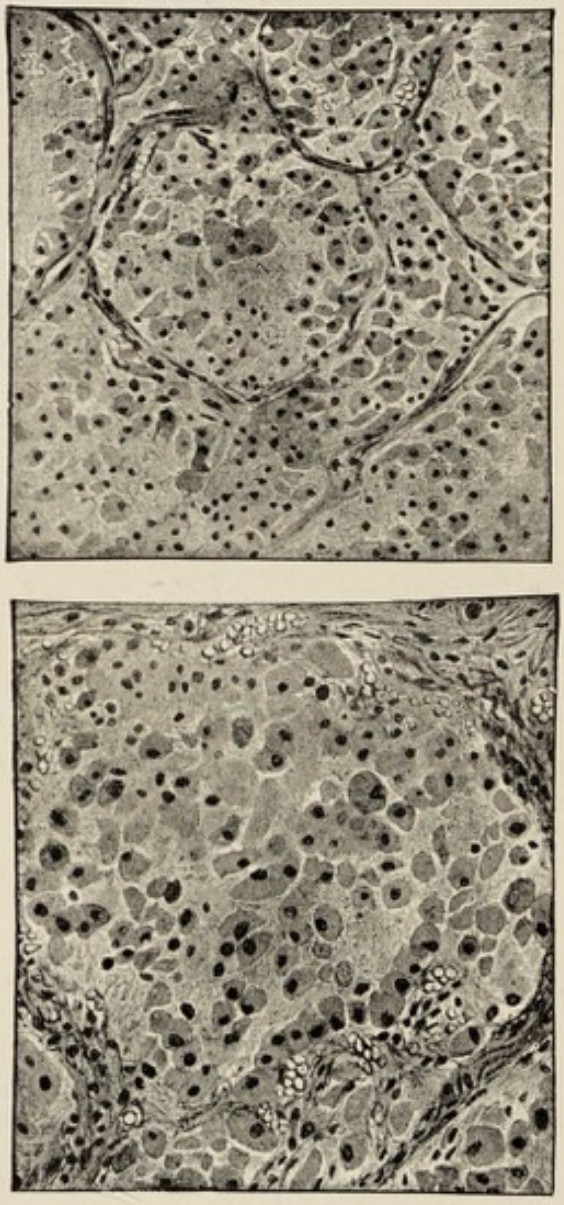


The upper figure shows compensatory hypertrophy in the thyroid gland of a dog 132 days after partial removal. The lower figure shows the thyroid gland from a case of Graves's disease.

the advantage of the thyroid gland of the unborn infant. This view is supported by the abnormalities found in the thyroid gland of the puppies of partially thyroidless bitches. Halsted found in the puppies of a bitch from which one lobe of the thyroid gland had been removed and which had been sired by a

dog that had also in part been deprived of its thyroid gland that the thyroid lobes in the puppies were 20 times larger than were those of normal puppies. I have repeated this experiment of

FIG. 19 AND FIG. 20.

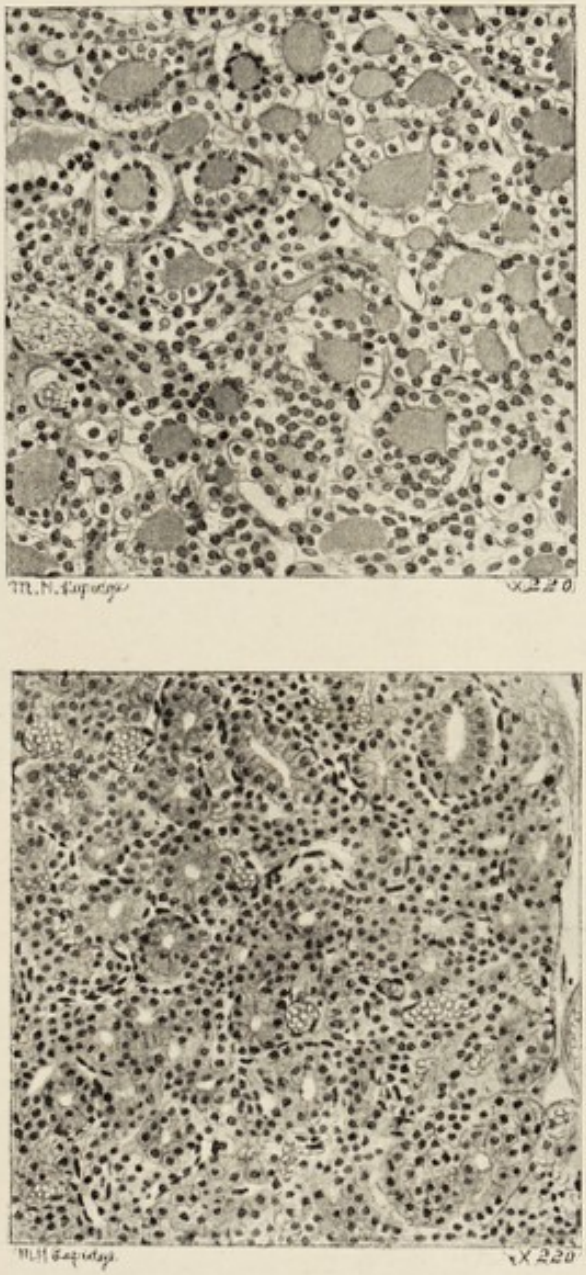


The upper figure shows the thyroid gland of a dog four days after partial removal. The lower figure shows the thyroid gland from a case of Graves's disease.

Halsted. From a bitch there was removed on one side the whole of one lobe of the thyroid gland, including the parathyroid glands, and from the other side nearly the whole lobe,

leaving, in fact, only one parathyroid gland and a morsel of the thyroid gland proper. Notwithstanding this extensive removal of thyroid gland it lived and about four months after the opera-

FIG. 21 AND FIG. 22.



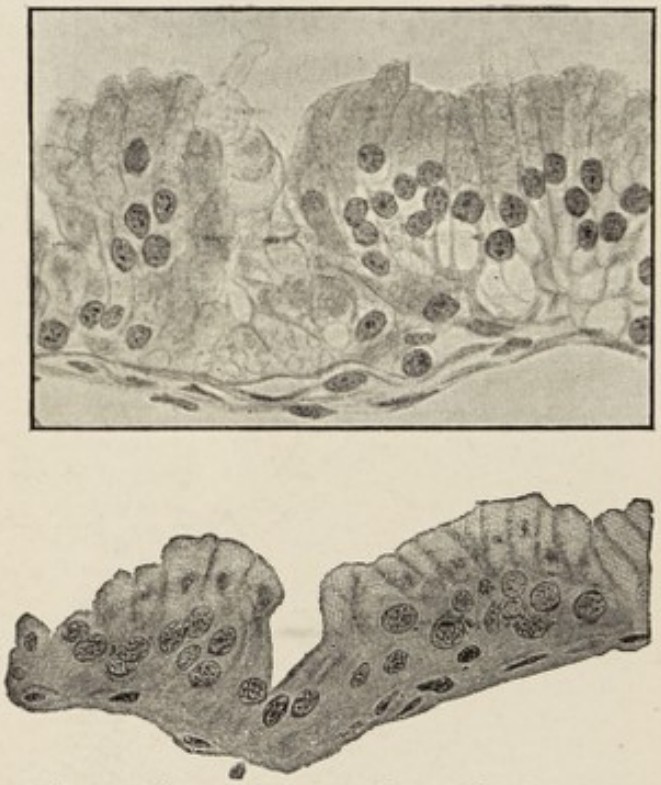
The upper figure shows thyroid gland of normal new-born puppy. The lower figure shows thyroid gland of puppy of almost wholly thyroidless bitch.

tion gave birth to a puppy. I found in the puppy that the thyroid lobes were large (at least they appeared so to me). On

microscopical examination it was found that there was an entire absence of colloid and that the secreting cells, instead of being cubical, were columnar; these are the changes of compensatory hypertrophy and are presumably due to an attempt to compensate for the absence of the thyroid gland in the mother.

Graves's disease has been treated by operative methods. These are mainly three—namely, operations on the cervical

FIG. 23 AND FIG. 24.



The upper figure shows the secreting cells in compensatory hypertrophy of the thyroid gland of a dog. The lower figure shows the secreting cells from the thyroid gland in a case of Graves's disease. (× 600.)

sympathetic, operations for diminishing the blood-supply to the gland by ligaturing some of its supplying arteries, and operations for the removal of portions of the goitre. The operations on the cervical sympathetic are based on the idea that these nerves are the starting-point of the disease. We have already discussed the question as to how far the thyroid gland is, and how far the nervous system is, the primary seat of the disease;

even if we decide in favour of the nervous system the question arises whether it is the sympathetic or the cerebro-spinal system that is at fault. The fact that the internal secretion of the thyroid gland can be sufficiently arrested by division of its supplying nerves to cause death shows clearly that there must be a centre for it in the medulla; we must therefore conclude that even if the nervous system is the starting point the fault lies with the cerebro-spinal system and not with the sympathetic. Still, even if the sympathetic is not the primary cause it may be materially involved in the evolution of the symptoms, and of this there is considerable evidence.

Of the five cardinal symptoms of Graves's disease it seems probable from the experiments related in the last lecture that the sympathetic has to do with the exophthalmos. The heart symptoms can be explained either by a continuous spasm of the accelerator nerves from the sympathetic or by a weakening of the action of the inhibitory fibres from the vagi. The latter seems to be the much more probable condition, but there is no reason why the two conditions should not co-exist. Indeed, von Cyon says that in the goitrous animals of Berne they both are present. As to the goitre, the secretory fibres to the thyroid gland would seem to come, as far as we know, by the cerebro-spinal and not the sympathetic nerves, and if so the sympathetic would have little to do with the enlargement of the thyroid gland. As to the blood-vessels, the goitre, as may be seen in the post-mortem room, is a very substantial thing, not to be explained by engorgement of vessels; moreover, the vaso-motor nerves in the sympathetic are constrictors, and would make the thyroid gland, if anything, smaller and not larger. The tremors and mental excitement in Graves's disease would be connected with the cerebro-spinal and not with the sympathetic system. Even if the sympathetic is the starting-point, it is necessary to consider whether any operation on it which would be likely to be beneficial is feasible. In the dog the augmentor fibres of the sympathetic are derived from the inferior cervical sympathetic and the annulus of Vieussens. As in man the third ganglion is behind the subclavian artery and the annulus round it, the operation for their removal would be extremely difficult, especially on the left side, for it must be remembered that the

operation has to be done on both sides. It is true that in man there are from the superior and middle cervical ganglia cardaic branches which may be augmentor, but as in the dog the augmentor fibres come exclusively from the lower part of the cord it is probable that in man they do so mainly. However, sympathetic operations, varying no doubt in extent, have been performed in man and we proceed to see with what results.

Boissou in a thesis for the M.D. degree of Paris has collected all the cases he could obtain up to 1898, and to them he adds a valuable critical study of the whole subject. Altogether Boissou has collected 27 cases, but four of these he excludes from analysis as they, for one reason or another, prove nothing. Of the remaining 23, 15 were well-marked cases of Graves's disease and eight ill-defined or *fruste* cases. Of the 15 well-marked cases two were cured, six were much benefited, three were slightly improved, and one received no benefit, while there were three deaths. Of the eight ill-defined cases one was cured, two were much improved, four were slightly benefited, and one was not benefited. By adding the two series together we get as a result of 23 cases operated on: three cured, eight much improved, seven slightly improved, two not improved, and three deaths. Boissou sums up thus: "Successes are rare; in cases benefited it is sometimes one symptom, sometimes another which is improved, and the improvement is sometimes immediate, sometimes late; sometimes there are relapses in the improvement. There are, too, cases of no improvement and cases of death. Neither by division, nor by excision, total or partial, have more brilliant results been obtained. From the physiological point of view, too, all is chaos. There is no agreement, no relation between the phenomena noted by the surgeons and those observed by the physiologists; also the surgical effects are in disaccord one with another." Finally, Boissou concludes: "If surgeons have been able by this new operation to modify Basedow's disease the results obtained have no constancy and are as much confused therapeutically as physiologically."

Considering the gravity of those cases in which the exophthalmos leads to ulceration of the cornea I have especially analysed the 27 cases of sympathetic operation collected by

Boissou with respect to the effect on the prominence of the eyes. Of the 27 cases seven must be omitted either because there was no exophthalmos to start with or because from some cause the record is imperfect. There remain 20 cases ; of these seven are said to have been cured of their exophthalmos, five were much benefited, seven derived little or no benefit from the operation as far as the exophthalmos was concerned, and in one subsequently to the operation both corneæ sloughed and the patient, who became blind, died from Graves's disease. This last case, and the seven cases in which no improvement followed show that the sympathetic operation is not a specific even for the exophthalmos. Also this last case, in which the patient lost her eyesight and finally died from severe Graves's disease 10 weeks after the sympathetic operation on one side and seven weeks after its removal on the other side, shows clearly that the sympathetic is not the *fons et origo mali*.

The subject of these sympathetic operations was dealt with by Mr. J. Berry in a discussion on a case of Graves's disease at the Royal Medical and Chirurgical Society last year. He expressed the opinion that the sympathetic has nothing whatever to do with Graves's disease and that the sympathetic operation should never be performed. He referred to Boissou's monograph and opined that those who would read it would agree with him ; that certainly has been the effect of its perusal on myself. There is, however, a small class of cases in which one might be tempted to perform a limited operation on the sympathetic ; I refer to cases of ulceration of the cornea. As these only occur in patients in whom the eyelids cannot be closed the complication must be due mainly, if not wholly, to irritation. Since division of the sympathetic will reduce proptosis, this operation might be tried in these cases, although, as we have seen, it was of no avail in preventing ulceration of the cornea in one case referred to by Boissou, that of Peugnier. I am not aware of this operation having been performed in any case with the express purpose of saving the eyes, but in one case it was recommended by Dr. G. Mackay to Mr. F. M. Caird, who, however, preferred to remove one lobe of the thyroid gland, which he did and with a most beneficial effect on the eyes.

The ligature of three of the four arteries to the thyroid gland is an operation which has met with a measure of success, but there may be a difficulty in reaching the arteries behind the enlarged thyroid gland. There remain to be considered the effects of removal of a portion of the enlarged thyroid gland. A considerable number of these operations have now been performed and have been collected, analysed, and considered by various writers. Allen Starr, writing in 1896, had collected 190 cases; 74 of these cases were reported as completely cured; 45 as improved; three as not improved; 23 patients died immediately or within a few hours of the operation; and of the remaining 45 no final report was available.

The occurrence of sudden death immediately after the operation or within a day or two of it is, as Allen Starr well says, a fact of very serious import; it constitutes a most serious bar to the performance of what would otherwise be a promising operation, and it is therefore well worth while to consider its cause. "Death after these operations," says Starr, "is not due to hæmorrhage or to any want of aseptic precautions. In all the cases reported there has been a sudden rise of temperature to 105°, 106°, and 107°; a very rapid pulse (180 to 200); extreme nervous excitement and restlessness with great anxiety and distress, profuse sweating, and finally collapse and death from heart failure." These distressing calamities have been attributed to various causes. Sometimes the anæsthetic has been blamed, but many of the deaths occur rather late for that, especially in the cases in which chloroform has been administered. It must, however, be admitted that animals suffering from athyroidea die very readily from chloroform unless it is administered with extreme caution. If the deaths are due to the general anæsthetic cocaine or eucaine can be, and indeed sometimes is, substituted. It seems, however, more probable that the fatal results are in some way due to the operation itself, and if that be so the most obvious and natural view is that the removed lobe is necessary to the life of the patient. Another view is that something goes wrong during the progress of the operation. It has been thought that the symptoms are caused by the handling of the lobe during removal, by which its secretion would be pressed into the lymphatics and thus into the

circulation, and that the incision into the thyroid tissue has led to a leakage at the time of operation and afterwards into the cavity of the wound from which it has been absorbed. In this way the cause of death would be an excess of thyroid secretion (normal or abnormal) in the circulation—hyperthyroidisation, in fact. Consideration, however, of the symptoms themselves would lead to the opposite view—that they are due to too little secretion in the circulation. Attacks of palpitation and dyspnœa, followed by collapse and death, we have seen to occur both in Sir William Stokes's case of acute athyroidea and in experiments on the lower animals. It is, of course, possible that in Graves's disease we have to do with an excess of one constituent of the secretion and a diminution of another, and that this latter condition is aggravated by the partial removal and constitutional disturbance during and after the operation.

Whatever may be their explanation, these cases are, no doubt, a great objection to operating, but they need not wholly turn us from that idea. It must be remembered that cases of sudden death occur in Graves's disease among patients who have not been operated on ; they are mentioned in all text books, and, in fact, are not uncommon. Also the prognosis to life in this disease is not at all satisfactory ; death has been recorded as occurring in six weeks from the onset, and even in the favourable surroundings of a hospital deaths do occur from time to time, sometimes suddenly without apparent cause, sometimes from diarrhœa or some complication. Indeed, it is from the cases of those patients who die in hospital that our knowledge of the pathology is mainly derived. What may be the subsequent history of the patients who return home is not certainly known ; some of them continue ill for a long time, others may no doubt improve, but it has been denied that cases of Graves's disease ever completely recover, at least without operation. Of the 190 cases of operation collected by Allen Starr 74 are reported as completely cured and 45 more as improved ; these results are very encouraging, as are also the records of individual cases. One of the earliest operations in Graves's disease was performed by Lord Lister when he was at the Edinburgh Infirmary. The patient was a woman, aged 26 years. She had been ailing for five years, during the last three of which she had

had well-marked symptoms of Graves's disease, for which, presumably, she had had medical treatment. It was intended at the operation to remove the whole of the thyroid gland (this was before the dangers of so doing were recognised), but this probably was not done. Before operation the pulse-rate was 130 and the pulse was irregular ; five days after the operation the pulse had fallen to 74 and was regular, and in a few weeks the exophthalmos was much reduced. The patient was seen again 10 years later, at which time she was suffering from phthisis. The exophthalmos was slight, the excitement of the circulation was nearly gone, and there was no thyroid tumour, but a slight eminence in the middle line suggested that a portion of the isthmus had been left at the operation ; there were no symptoms of myxœdema.

As another example a case recorded by Reidel may be mentioned. The patient, a female, aged 20 years, had suffered for years from a goitre and during the later years there had been in addition palpitation so severe that she complained that her heart seemed trying to jump out of her chest. Exophthalmos was so extreme that it was noticed in the street, and the patient had become extremely nervous, depressed, and much emaciated. The right half of a parenchymatous goitre was excised ; the case did well. Three years after the operation the patient was seen again ; she was in good spirits and in full enjoyment of life. The palpitation was completely cured, she could walk for an hour at a stretch, and at a ball could take part in every dance. The exophthalmos and emaciation were gone.

A case in a male under Sir William Stokes's care may also be cited. The patient was a farmer, aged 32 years, who seven years previously had had a fright caused by seeing a friend killed by a threshing machine. Three weeks after this he noticed a slight enlargement in the neck, which was followed by palpitation and exophthalmos. These symptoms continued, together with other characteristic symptoms. Six years later he was admitted to hospital where under treatment he improved, but on returning home he relapsed and was again admitted to hospital, when Sir William Stokes was asked to see him. Operation was decided upon and a central tumour of the size of a Tangerine orange was removed, together with part of one lobe.

In a few weeks there was marked alleviation of all the symptoms and the patient ultimately recovered. Two years after the operation there had been no recurrence of the symptoms.

My own experience is confined to two cases. In the first the patient was very ill, palpitation and dyspnœic attacks being the main symptoms. As she continued to get worse operation was decided upon and the right lobe of the enlarged thyroid gland was removed. The patient got much better and all the symptoms were greatly relieved, but there are still (it is now eight years since the operation) symptoms of the disease. The other case was much less severe. The symptoms, however, did not yield to medical treatment, and as there was a uni-lateral swelling operation was decided upon. The swelling proved to be due to an adenoma, which was excised. The symptoms completely disappeared; indeed, the tremors had gone the day after operation, and the patient remained quite well, at least for some months. Great improvement in Graves's disease after removal of an adenoma has been noticed before. Murray records, too, a case in which the symptoms almost completely disappeared after drainage of a cyst in a goitre. In the case just mentioned the adenoma was found to have undergone the usual changes seen in Graves's disease; the rest of the thyroid gland was little if at all enlarged. Many other cases very encouraging as to operation could be cited. Probably the lesson to be learnt from the fatal cases is not that operations should not be performed, but that they should be performed earlier.

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