THE BRADSHAW LECTURE

ON

SOME DISEASES OF THE THYROID GLAND.

Delivered before the Royal College of Physicians.

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[PROFESSOR GREENFIELD first referred to the death of the late President, whose great consideration and thought he had experienced in connection with this lecture.

He then referred to the great and rapidly growing importance of the diseases of the thyroid, especially, but not solely, myxœdema, since many others not yet accepted might also probably come under the head. Instead therefore of going more widely into the subject of the pathology and physiology of the glands, either of which might have afforded much material, he proposed to speak of Graves's disease and Basedow's disease as if it were possibly a primary disease of the thyroid.

In so doing he was not acting upon any hasty or recent change of opinion—for ever since he had studied myxœdema first in Dr. Ord's early cases he had been struck with the antithesis afforded by it with exophthalmic goitre. And since ten years and a-half ago, when a fatal case under his care afforded him the means of making a fuller research, he had formed the views and constantly taught the facts afforded by a continued series of observations.]

In thus discussing Graves's disease, even provisionally, as a disease of the thyroid gland rather than of the nervous system, I am aware that I am opposed to nearly all English and American physicians of eminence. It is only necessary to look into the more recent writings of my friends Drs. Bristowe, Hughlings Jackson, Gowers, Osler, and others, to see that this relation is usually either ignored or rejected.

The only physician of any authority who has to my knowledge expressed similar views based on the clinical contrast is Dr. Byrom Bramwell.

On the other hand several foreign authors, especially Th. Wette, Möbius, Joffroy and Achard, and J. Renant, have adopted views somewhat similar to my own.

Seeing then that my object is rather to marshal the facts which bear upon this question of the thyroid origin of Graves's disease than to enforce any dogmatic conclusion, I shall classify them under the following heads:—

1. The examination of the thyroid, which so far as I have been able to obtain material reveals in nearly all cases a peculiar form of proliferation of the gland tissue, unlike that seen in other goitres, and resembling a proliferation for the performance of increased function.

2. The relief afforded by removal, partial or entire, of the gland.

3. The presence in the nervous system of changes, slight in degree, but widespread, especially affecting those centres or nerves which we should suspect from the symptoms to be involved. The fact that these alterations are of a like nature to those seen in toxic diseases, for example, hydrophobia and tetanus, suggesting that they also may be of toxic origin.

4. The contrast, in many of the leading conditions, of myxœdema and Graves's disease, these including both symptoms and anatomical changes.

5. The correspondence, in some important respects, of the phenomena of Graves's disease with those produced by artificial introduction of thyroid secretion.

Changes in the Thyroid Gland in Graves's Disease.—Of all the remarkable facts in connection with the history of this disease, the most striking is the apparent neglect of the direct study of the changes in its structure of the thyroid gland itself.

[How little attention was paid to the condition of the gland itself at a comparatively recent date is shown by the discussion at the Ophthalmological Society in 1886 (*Trans. Ophth. Soc. of Great Britain*, vol. vi,

1886). In the circular of queries, the only question is as to equality of enlargement on the two sides. I do not find any reference to the possibility of functional derangement of the gland as a cause. Of the fatal cases recorded, the following brief outline of post-mortem results may be given: Dr. Bristowe, four fatal cases: (1) Thyroid slightly enlarged; no disease of nervous system. (2) Thyroid much enlarged, especially the right lobe. (3) Lateral lobes larger than natural. (4) The isthmus had been removed to relieve pressure some months before death. Goitre small. Dr. Wilks mentions one fatal case. No mention of microscopic examination. Dr. Samuel West, two cases in which post-mortem examination. Case 37, condition of thyroid not mentioned. Case 38, "post-mortem examination negative." Mr. C. Higgins, one case in which post-mortem examination made by Dr. Goodhart, "enlargement of thyroid." Mr. Quarry Silcock, one case. Thyroid weighed 4½ ounces. The section resembled one across the fibres of the gluteus maximus, but paler. Overgrowth of the interacinous connective tissue, extensive proliferation of the acinar epithelium, nervous system normal. It is important to note that the disease had lasted twelve years before the fatal issue. Thus there is only one case mentioned in which a careful microscopic examination is recorded, and in describing this no reference is made to the presence of any large amount of newly-formed gland tissue, though it would seem probable that it was present.]

Changes are indeed described by various writers, but for some years at least there appears to have been little or no application of our improved methods to the study. In many most valuable papers, even to the most recent, either no mention whatever is made of the nature of the changes visible to the naked eye or with the microscope, or they are disregarded, and the disease attributed to the nervous system. It may be that I have overlooked some important paper, but as I have been seeking evidence for several years, and have been constantly disappointed, and as careful writers repeat the same statements as to the nature of the changes, I cannot think that those I have observed are generally recognised. And whilst the material at my disposal is limited in extent, being derived from only six fatal cases, the constancy in the general character of the changes, and their total deviation from those usually alleged to exist, make me regard the observations as of some importance. The long intervals of time between my fatal cases and their small number, have prevented me from doing more than form and mention in teaching the views I have long entertained, waiting for more extended observations before publication.

Most writers, if they refer to the gland at all, adhere to the view that the enlargement is consequent on and associated with active hyperæmia and vascular dilatation. Thus Ziegler, in his textbook on *Path. Anat.*, 6th edition, p. 723, speaks of the chronic enlargement of the thyroid, "which occurs as a symptom of that peculiar neurosis of the vessels described as Basedow's disease," as a condition due to congestive hyperæmia; and he adds that it is in accordance with the view that the excessive blood supply is the cause of the overgrowth, that there is an abundant vascularisation found in the growing gland tissue.¹

Taken in a certain sense, but not in that evidently intended, it is no doubt true that a proliferation of blood vessels does occur, as in all active hyperplasia of glands, as also of other parts. But so far from this vascularity being excessive, it has not been specially prominent in any case I have seen. In one case there was very slight vascularity towards the surface of the lower lobe. The enlarged gland, which may be many times its normal bulk, is, on section, of pale pinkish colour, and so closely resembles in appearance a salivary gland, that a portion may readily be mistaken for one. A few cysts, usually minute, may be present, containing usually a clear serous fluid, but they may be absent entirely, and are relatively less frequent than in mammary or other glandular tumours. Most of the substance is comparatively solid but elastic, and of far less consistence than the normal gland.

In shape the enlargement in typical cases differs from most others from the fact of the gland being usually more uniform, its varieties partly depending on the normal marked variations in shape of the gland. I do not assert that this need always be so, for the degree of change usually varies in different parts. Microscopic examination shows that the enlargement is due to an enormous hyperplasia of the secreting structure. It bears to the normal gland the same relation which the mammary gland in lactation bears to that in quiescence. In no other way can we account for its condition, or find any analogue than by such a comparison, for whilst, as in all such hyperplasias, we may find, especially in ductless glands or glandular tumours, some tendency to cyst formation, this must occur from the physical condition.

I have sought in vain for any *post-mortem* evidence of absence of enlargement, or marked change in the thyroid, accompanied, as it must be to be of any value for scientific purposes, by microscopical examination. It is true that the enlargement may be so slight as readily to escape detection during life. I had under my care, two or three weeks ago, a most marked case of the disease, in which the thyroid is situated so low, and its enlargement is so slight, that but for very careful examination it would have been overlooked. But from what we know of like changes in other organs, it is evident that altered structure, and not size, is the test of disease. Failing this evidence, we have nothing to oppose to the positive argument from actual observation.

The more striking changes in the thyroid are two; closely allied in nature and usually existing in an especially marked manner in different parts of the same gland.

Both of these changes exactly correspond to such as may be seen in a gland in active evolution, and, if we except the development of an adenoma, have no other pathological equivalent.

Associated with these changes we usually find no increase in vascularity but rather a diminution, although there can be little doubt that the proliferation of the tubules is associated with a corresponding evolution of capillaries.

A comparison of these changes with those found in the development of adenomatous growths in the thyroid reveals striking differences.

The change is a general one, not localised, and spreading in a tumour-like manner. Moreover, the regular mode of evolution, and the absence of the irregular growth, and filling of the tubes with cells of irregular size and shape, is distinctive. I do not say that some adenomas of the thyroid

Plate A.—Normal, 40 diam.

That which appears to be the earliest is an alteration in the character of the epithelium lining the spaces from a cubical to a columnar type. This change is associated with greatly increased proliferation, similar to that seen in adenomas, so that papillary projections into the spaces are common. In this condition, the resemblance to a cystadenoma of the ovary is striking. In addition, there appears to be active secretion, and² absorption of the colloid material, which is replaced by a more mucinous fluid. Desquamation of the altered epithelium is also common, the masses of columnar cells lying free in the space, which may be dilated. It is observed that the glandular character and arrangement is not lost.

With this, there may often be seen elongated duct-like spaces, which suggest the idea that there are ducts in the gland.

The second change is the production of an enormous number of newly formed tubular spaces, lined by a single layer of cubical epithelium. In their structure, and the regular arrangement of their epithelium, they exactly correspond to the tubules of a secreting gland, for example, the sweat glands.

Plate B.—40 diam. Catarrh from septicæmia, disappearance of "colloid."

may not show a similar structure, but I have been unable to find them in the cases I have examined.

As a sequel of these proliferative changes we may find catarrh. This is sometimes prominent in advanced cases. The epithelium desquamates, undergoes cloudy swelling, and here and there may fill the tubules. This is especially seen where death has occurred with high temperature.

From the study of cases of long duration, it appears that this proliferative change is liable to be followed by fibrous overgrowth. At first there is little sign of this. The fibrous septa, which are little prominent in normal conditions, may show some thickening at a comparatively early date. But within the lobules no such change is seen. In advanced cases the fibrous overgrowth, starting from the septa, invades the glandular structure, and in parts completely obliterates it. The lining epithelium undergoes atrophic changes similar to those seen in all interstitial overgrowth in glands. It becomes small, separates from the subjacent tissues, and then disappears entirely.

Two points deserve mention. In the normal structure of the thyroid we find a number of undeveloped glandular spaces, often in clustered masses. This suggests that nor-

anally there exists, as has been shown to be the case in other glands, a reserve of secreting tissue capable of development in accordance with physiological needs, and probably always used up during the course of life. The absence of increased vascularity, in fact, the apparent diminution in the vessels, is a point of great practical importance. For there is no doubt that the idea that the thyroid was especially vascular in Graves's disease has been one great deterrent to the surgeon against operation. The cause of the apparent vascularity I shall discuss later.

In conclusion, I would suggest that since the change in the thyroid in typical cases of Graves's disease corresponds so closely with that seen in glands undergoing evolution for increased function, it must have some profound effect both on the quantity and quality of the secretion.

Now it is true that we could not, from the study of this condition alone, determine the effect on function. If we re-

present without notable increase in volume. It may well be that it is in those cases in which catarrhal and cystic changes are least prominent the activity of secretion is greater than where the derangement of proportion in size is greater. The intensity of the symptoms certainly bears no proportion to the actual size of the gland, some of the severest cases being where it is only moderate in degree.

Vascularity of the Thyroid.—It has been alleged by some that the enlargement of the thyroid is caused by excessive hyperæmia, and also that in Graves's disease it is always highly vascular. If the thyroid enlargement is due to excessive vascularity, how comes it that no similar enlargement, that is, with proliferation, occurs in other adjacent parts or from experimental hyperæmia? The concentration of the hyperæmia should surely suggest that if it exists there must be some special relation between the gland and the vasomotor changes. Whatever hyperæmia may exist, in

Plate E.—200 diam. Graves's disease, Case II. Character of villi.

garded the change as catarrhal, we should anticipate alteration in the secretion, perhaps with excess in quantity, almost certainly with defect in quality. But a study of other conditions of its enlargement, the contrast afforded by the reversed condition in myxœdema, and comparison with other glandular enlargements convinced me that this could not be the essential condition. In a series of cases, not of Graves's disease, which I have had opportunities of observing marked enlargement of the gland has occurred during pregnancy, subsiding either during lactation or later. And in one or two cases the presence of enlargement in persons with an unusually large thyroid has been noticed to concur with increased rapidity of pulse and a slightly elevated temperature, only, however, from one- to two-fifths of a degree, but persistent. And here I may note that such minor degrees of enlargement and variations in size are by no means infrequent in women, and deserve careful study.³

I would especially emphasise the point that it is not the mere size of the gland which is of importance, but its structural alterations. For it is quite possible that hyperplasia of the kind I have described, a great alteration in the amount of secreting tissue and greatly exaggerated function may be

Plate C.—40 diam. Graves's disease, Case III. Low power to show general character.

so far as it is not such as is seen in the mammary gland during lactation, it shares with other parts, and neither in physiology nor pathology do we find that hyperæmia alone affords any parallel in the production of such changes.

Apparent Increase in Vascularity of the Thyroid.—It appears to be commonly accepted that the thyroid actually pulsates in Graves's disease. I have carefully examined many cases, and have failed to find any sufficient evidence of this.

The pulsation is far more marked over the arteries than elsewhere. A thrill may often be detected over the superior thyroid artery when it cannot be found elsewhere, and a general thrill I have never seen. The apparent thrill appears to me to be due to the relaxation and enlargement of the arteries. It has been shown that the arteries actually enlarge, and may undergo irregular dilatation. But this enlargement of nutrient arteries is also seen in all active hyperplasias. For examples, the mammary and uterine arteries may be cited.

Added to this, we have the pressure both on arteries and veins which must undoubtedly occur. The carotid and its branches must be compressed and stretched, and commu-

nicate their pulsation in an abnormal degree. The internal jugular and the plexus of veins over the thyroid must also be compressed. Indeed, it has been suggested that by its pressure on the jugular the thyroid controls the vascularity of the brain—an hypothesis in which I do not concur. But, if the pulsation is only in the vessels, why does not the same phenomenon occur in ordinary goitre? The explanation seems to lie in the relaxed condition of the arteries, which may produce a murmur in the other great vessels, heard over the sternum; and also in the fact that the veins are engorged, not from pressure alone, but from the active changes in the thyroid, just as the mammary veins are engorged during lactation. Except in cases in which, through cardiac valvular disease, or dilatation, venous pulsation existed in all the visible veins in the lower part of the neck, I have never been able to detect any pulsation which could not be accounted for by these causes.

Plate D.—50 diam. Graves's disease, Case I. Showing tendency to minute cyst formation.

Amongst the objections to the view that the change in the thyroid has any special causal relation to Graves's disease, is that myxœdema has been stated either to co-exist with, or to follow the former.⁴ The fact that it is apparently infrequent, and that rapid subsidence of the enlargement may occur, are additional arguments in favour of the view that the hyperplasia is rather functional than inflammatory, that is, that it is governed by the laws regulating evolution for increased functional activity.

But I must add that I have rarely seen complete subsidence without any induration. Nor can I concur in the view that the enlargement usually or even commonly occurs in the course of Graves's disease, the thyroid being previously healthy. My own experience suggests that some enlargement commonly precedes, it may be for some years, the more rapid enlargement and greatly exaggerated function, which may be called into existence by some sudden exciting cause.

Some writers confidently allege that Graves's disease may exist without enlargement of or marked structural change in the thyroid. As regards the alleged co-existence of myxœdema and Graves's disease, it would be especially interesting

to know whether the Graves's disease was first in order of occurrence. I have not been able to examine the records of alleged cases. But the fact that in some long-standing cases of Graves's disease we may find so extensive fibrous and atrophic changes raises the question whether increase of activity in the functions of the gland, if the cause of the disease, must necessarily persist, or whether persistent changes in the nutrition and structure of the nerve centres, due to prolonged irritation, may not keep up some of the symptoms; if so, there would be nothing contradictory in the persistence of these together with the phenomena of myxœdema.

Relation of other Forms of Goitre to Graves's Disease, especially with Reference to Operation.—In comparing the current expressions of opinion on the relation of thyroid enlargement, no fact is more striking than the existence of two opposite views, and the fact that many writers appear to accept both views, though they appear to me highly inconsistent. One view is that there need be no change at all in the thyroid; that all the phenomena are of primarily nervous origin. Thyroid change, if it exists, is regarded as only one of a group of secondary changes. The other view, which seems to be that especially adopted by surgeons, is that any kind of goitre may cause either the complete disease or only those imperfect forms which manifest one or more of the leading phenomena, especially tachycardia; and the tendency is to explain these symptoms by the pressure results. Only by a complex process of argument, and by omitting some points in favour of each view, can these be brought into harmony. The old sympathetic theory is the nearest approach to a consistent view, but it fails absolutely to explain why, on the nervous theory, the peculiar and special change in the thyroid should be produced.

It is true that some of those surgeons who have paid most attention to goitre in all its forms have been led to adopt a view much in accordance with that which I have been urging—namely, that the symptom complex is the result of some irritant poison generated in the thyroid. Notably, Th. Wette, whose very large experience of all forms of goitre makes his conclusions of especial value, has argued in favour of this view. His valuable paper⁵ should be read by all who seek the latest information of the facts from the surgical point of view.

I can only refer cursorily to observations on such occurrence of some of the phenomena of exophthalmic goitre in cases of other chronic goitre, referring you to fuller information to such papers as his. But whilst we must take all the facts into consideration before arriving at conclusions on the pathology of the disease, yet it is obvious that the cases with which we as physicians are familiar are not of this type. The fact that the cases which come under our observation are of fairly uniform type and history, that the course of the disease and the possible great diminution under treatment are unlike the course of cystic or adenomatous goitre, and that the remedies which are efficient in endemic goitre are found useless in this form, all lead us to believe that we are dealing with a special and peculiar disease. Moreover, the large degree of correspondence in the changes found in the thyroid in such examples as I have brought forward, and in other cases where the record of the examination of the thyroid has been complete,⁶ all point to the same conclusion. So that, in so far as corresponding symptoms may be produced in other forms of goitre, we must regard this special form as affording a clue to the others. The very fact of the extreme rarity of such symptoms, even to an imperfect degree, in common goitre, is opposed to the view that other enlargements or changes in structure, however great, are alone efficient to produce the disease. When, therefore, such symptoms do arise in connection with other goitres, we may reasonably suppose that they also depend on the accidental presence of corresponding changes in function, possibly also in structure, to those in the more special form.

Examination of some goitres—unfortunately only a few at present—has shown me that the structural changes in different parts of the same thyroid may be of very various type; hence an examination of only one part is of little value. The only direct observation on the structure of a localised chronic enlargement with exophthalmos which I have been able to make is in a case in which my friend, Mr.

Francis Caird, removed the right lobe of the thyroid for a great and chronic enlargement. Some symptoms of Graves's disease were present, but I have not yet seen the complete record. On examining a portion of the thyroid the most striking fact, as compared with other common goitres, is the presence of an enormous increase of small spaces, instead of the usual great enlargement of nearly all. The change appears, in fact, to be one of great increase of the normal structure, with, upon the whole, a relatively normal, though actively developing, gland structure.

If we accept the view that the colloid material is the active ingredient in the thyroid secretion, this case would suggest an enormous increase of thyroid activity. But even without this view there are appearances suggesting a great and, apparently, increasing activity of secretion. If such were the case it would tend to support the view that this alone may be the cause of Graves's disease.

One cannot, upon so slight grounds, infer that this is the condition in all the cases of common goitre associated with Graves's disease, but it suggests a fuller research into the cases of this kind.

OPERATIVE TREATMENT.

In investigating the literature of surgical interference in exophthalmic goitre great difficulty is met with, owing to the fact that the cases are often so imperfectly recorded or that the presence of a moderate degree of tachycardia has sufficed to cause a case to be recorded as one of Basedow's disease. One very important practical conclusion from this is that the statistics of recovery after operation for Graves's disease are unreliable as a guide to the physician in recommending, and the surgeon in performing, operations for partial removal.

In spite of this the number of cases fully recorded, and undoubtedly true cases, in which cure of the disease has resulted is sufficient to encourage operation, and the small mortality in cases treated with strict antiseptic precautions removes one great objection to operation. In no case which I have found recorded did any excessive hæmorrhage occur from cutting through the gland itself, the chief source of hæmorrhage being the enlarged veins on the surface and the comparative abundance of small arteries around the gland.

It was my purpose to give some details of the recorded cases, but, since the subject has been so fully studied in Wette's recent paper, I need not do more than refer to it.⁷

It has proved unnecessary to remove the entire gland. Removal of one lobe, or even, in some cases, of the isthmus or some especially enlarged portion, has sufficed, not only to arrest the symptoms, but to cure the disease.

In some cases the exophthalmos has disappeared almost immediately after the operation—a fact strongly antagonistic to the view that it depends on increase of orbital fat. Indeed, the observations in favour of this theory are so open to doubt from various points of view that it is surprising that it should ever have been seriously entertained.

OBSERVATIONS ON THE NERVOUS SYSTEM.

In considering the phenomena usually attributed to the nervous system it is obvious that I cannot, in the time at my disposal, review, however briefly, the numerous and conflicting theories as to the cause or site of their production, the observations by which they are supported, or the history of the changes in the theories predominant from time to time.⁸ It must suffice to remind you that whilst the sympathetic, especially in the cervical region, was formerly regarded as the chief site of the lesion, further consideration led many authorities to shift the site to the vagi, and later to the medulla oblongata. More recently it has been found necessary to acknowledge that, in order to account for hysterical and emotional disturbances, etc., and for mania, we must regard the higher cerebral centres as in some way involved; but in what region, and of what nature, the changes are hardly any two authorities agree.

Such observations as have been made of the existence of definite lesions in the nervous system, whether central or peripheral, have, even by the observers themselves, been often regarded as accidental, or others have shown that like changes may occur without analogous symptoms, and in other diseases.

Before entering upon the actual observations, it is well to suggest one or two general considerations.

First, that in the present state of our physiological knowledge, we meet many problems which involve the solution of points which physiologists acknowledge to be unsettled, and the results of experiments are as yet conflicting. Such are the nature of cardiac innervation, and the results of section or irritation of various nerves on the heart's action. When we find that it is regarded as doubtful whether there are intracardiac ganglia, and that the distribution of the nerves differs so much in different animals, and so on, we may well be cautious as to the results of experiments on pressure on parts of the vagus and sympathetic, or the supposed effects of their irritation.

Secondly, that as regards some of the phenomena usually attributed to the nervous system, their analogy with the phenomena produced by some drugs lead us to believe that they may be equally explicable by direct effects of local irritation of a toxic nature, or by other factors. Under this head come tachycardia, arterial parietic dilatation, etc.

Thirdly, that on a general view of the nature and mode of occurrences of the "nervous" phenomena, it appears that they are, with one or two exceptions, liable to rapid alteration. For example, in one recent case of my own, there occurred, in rapidly alternating succession, irregular elevations of temperature, ophthalmoplegia, varying from day to day in degree and localisation; polyuria, albuminuria, each only lasting for a day or two, and recurring at intervals; diarrhoea of great severity, unilateral sweating, and various other phenomena, the only persistent symptoms being tachycardia and exophthalmos. Even the two latter symptoms showed remarkable variations within brief periods; so also did the tremor, which was very marked, and the great excitability and rapid and sometimes confused speech.

From such facts we might well suspect that whatever changes might be found in the nervous system would probably be of such minute and transient character, that only by very minute and widespread examination could they be detected. Indeed, one would say that unless they caused permanent degeneration of some of the tissue elements, we might not be able to detect them by our present methods.

When, therefore, actual lesions are discovered after death, especially where any definitely localised nervous phenomena have immediately preceded death, or, as with hyperpyrexia, have been its cause, the discovery of such lesions is of prime importance. Let me remind you that even in hemiplegia, and in some cases of spinal paralysis, no change may be discovered. Moreover, if the cause of nervous lesions is a generally acting one, we need not exclude from its operation either the sympathetic, the peripheral nerves, or the ganglia.

Not only have such changes been recorded by others, but I have myself some actual observations. And I hope to give some evidence that these lesions are especially observed in those regions or centres of which the function is especially impaired. Moreover, that in their nature, and to some extent in their distribution, they correspond with those seen in tetanus and hydrophobia—a fact which, taken in conjunction with other considerations, suggests that they depend on a toxic irritative action.

If time permits I hope to show that from comparison with the nervous system in myxœdema, which are in some parts of an opposite nature, it is not improbable that the irritative lesions in Graves's disease especially affect those parts of the nervous system which are normally most dependent on the thyroid secretion for incitement to normal function; that the absence of the secretion leads to atrophic changes, whilst excess or alteration of the secretion leads to irritative and toxic phenomena. But, since time forbids a detailed statement of these changes, I must reserve them for the microscopic demonstration.

NERVOUS SYSTEM.

Cervical Sympathetic in Graves's Disease.—Although I have examined the cervical sympathetic in four cases of Graves's disease, there are only two which have been examined by modern methods, and can be referred to with confidence. In this examination, owing to the way in which the nerves were removed, it is difficult to localise exactly the site of the changes. But I have made sections in various parts, both of the ganglia and the nerves, by transverse and longitudinal sections. The middle cervical ganglion and the parts adjoining have been those especially studied.

Very marked changes have been found. The ganglia have appeared to be somewhat swollen. Marked hyperæmia, especially in the more superficial parts, but not limited to them, has been constant. In the most marked case, from which most of the sections shown are taken, the principal changes found were:

1. Presence of subacute inflammatory change, evidenced by leucocyte emigration from the minute venules, and their marked hyperæmia.

2. Active invasion of the tissue by leucocytes, which especially invade the spaces in which the ganglion cells lie.

3. Degenerative changes in the ganglion cells, which appear to be invaded by leucocytes. In some of the cells, however, more passive degeneration was seen.

The longitudinal sections of the sympathetic cords showed much less marked change.

From a comparison of these changes there can be no doubt that the sympathetic ganglia are the seat of a subacute inflammatory process. It may be fairly assumed that this leads to changes in function, either by irritation or by degeneration. The contrast of similar parts in myxœdema is very striking.

In myxœdema the ganglia appear much smaller than in Graves's disease, when corresponding parts are compared. The principal changes found are:

1. Marked interstitial fibrous overgrowth, especially at the peripheral parts, where, on transverse section, ingrowths of fibrous tissue are seen. On longitudinal section, also, bands of fibrous thickening are seen, especially along the nerve bundles.

2. Degenerative changes in the ganglion cells. These are, for the most part, of the type seen in chronic degenerations, and are accompanied, in many parts, by marked pigmentation.

I have not seen any sign of myxomatous degeneration in these parts. For purposes of comparison I have shown alongside these the degeneration consequent on the invasion by new growth.

Central Nervous System in Graves's Disease.—The parts especially examined have been the pons and medulla in two cases. I regret that, owing to the long time since I examined these parts and the methods employed, many have deteriorated, and that many of the sections have been mislaid. I can, therefore, only show some of the more prominent changes. These are seen throughout the pons and medulla, but are especially to be observed in the medulla oblongata. They are closely analogous to those seen in the sympathetic ganglia. In various parts, especially in close relation to the ganglion centres, there are here and there dilated vessels filled with leucocytes, some of which are escaping or have escaped into the surrounding tissue. Together with these minute hæmorrhages are frequent. Many of these are so minute as to escape detection unless examined with a high power. When thus examined, some of the microscopic hæmorrhages are found to be in process of absorption. In addition to these, in one fatal case with high temperature, numerous small hæmorrhages were found in the floor of the fourth ventricle but not limited to it.

In many groups of ganglionic cells examined some of the cells were found to be in process of atrophy. This was of a kind allied to cloudy swelling, one or two cells in a group examined being found swollen, the nucleus invisible, and the protoplasm staining imperfectly. In some cells a sort of vacuolation was seen. The fact of the presence of these changes suggests that a slight and persistent condition of irritation, with subacute inflammation in parts, was present. I should add that the changes were not confined to the centres, but that patches of leucocyte emigration were seen here and there in some of the nerves shortly after their emergence from the brain.

I have not been able to make a sufficiently exhaustive examination as yet to determine which nerve centres were especially affected. The changes seen resembled in general character those seen in tetanus and hydrophobia, less in degree.

It was my intention to enter somewhat fully into the changes found in the central and peripheral nervous system in myxœdema, and to contrast and discuss their bearing on the pathology of the disease. Time forbids more than a

demonstration of some of the more characteristic. In all of five cases examined very marked changes were found, of a degenerative nature, especially in the nerve trunks of the lower limbs; and whilst they were irregularly distributed, I think they were most abundant in some nerves, for example, great sciatic, than in others. Nor is it possible for me within the time to discuss the many interesting questions as to the intimate causation of tachycardia, exophthalmos, etc. Physiological experimenters, with few exceptions, regard exophthalmos as due to irritation of the sympathetic, with or without some abnormal condition of the muscle of Müller.

TACHYCARDIA.

But tachycardia has received many explanations. Irritation of the sympathetic, pressure on the vagus, central change affecting the controlling centres in the medulla oblongata, etc., have been invoked. But there are two other possible causes or adjuncts. One is the parietic dilatation of the arteries, the other a possible direct irritation of the muscle of the heart. Owing to this the heart muscle may be in a state of abnormal excitability corresponding to that of an irritable muscle. In other words, it may not be a nervous phenomenon at all. I regret that time forbids me from bringing forward facts bearing on these questions.

Antithesis of the Clinical Phenomena of Myxœdema and Graves's Disease.—It seems needless to dwell in any detail on the contrast presented by the symptoms and general conditions of the two diseases, since they are obvious to all who have compared them. The one (Graves's disease) occurs, especially in females, at the age of greatest activity of the generative organs, of increased excitability, of nervous tremor, of tachycardia and ready mobility of the arterial reflex, of liability to exaggerated temperature from slight causes, and still more in febrile diseases, of ready and excessive perspiration, of altered vascularity and nutrition of the skin of an opposite character to that in myxœdema, of excitable and active mental condition, and the frequent presence of amenorrhœa. In myxœdema we have the occurrence in women, especially at the period of menopause, abnormal diminution of excitability where mania is absent, stolidity and slow movement, and absence of tremor (except in the very rare cases of tetany), of slow action of the heart and unexcitable pulse, of abnormally low temperature in ordinary conditions, and of a such a degree of immobility of the heat-controlling centres that the course and phenomena of febrile diseases are either largely altered or suppressed, the absence of even normal cutaneous transpiration and the difficulty of exciting sweating, the changes in the skin and subcutaneous tissue leading to a chronic dropsical condition, the large abeyance or slowness of thought and expression, the altered speech, and the frequent presence of menorrhagia.

In the form of mania there are also differences, for while in Graves's disease the tendency is to active mania, in myxœdema the commonest form is similar to that sometimes occurring in association with cardiac failure, depression, delusion of melancholic type, etc., being commonest. It is true that we sometimes meet with mania of more active type, that in some of the milder forms there are exalted delusions, and that during the periods of mental symptoms we may find the patient in a very happy frame of mind, the speech may become rapid, although it still exhibits the tendency to the use of periphrases and long words which indicate difficulty in verbal expression of ideas; and that in the more severe conditions there may be very great violence, periodic exacerbations, etc.; in others the mania may be recurrent and suicidal. Yet on a general view, we find that in myxœdema it corresponds with those forms of insanity associated with malnutrition, and although we cannot draw any such sharp line of contrast in individual cases, yet, on comparison of the general tendency, we find that in Graves's disease there is a greater tendency to acute delirious mania, or to a type approaching choreic mania, while in myxœdema this is rarely present.

There is another point of contrast which I am inclined to regard as of some importance—namely, the great tendency in myxœdema to tuberculosis; of course, it may occur in Graves's disease, but, so far as I can judge, there is no

especial tendency to it. In myxœdema it is especially frequent. Of the fatal cases under my care, and in two of those which I have, through the kindness of friends, been able to examine all the organs, tuberculosis widespread and advanced was present in five out of seven cases, and in one case of sporadic cretinism. In all the symptoms were marked, and the temperature greatly modified. In three of these cases the tuberculosis was remarkably widespread. On the other hand, it was very slow in progress, and in one case the tuberculosis in the lungs had undergone an almost complete cure before death. In one other fatal case, which was long under my care, and died soon after leaving the infirmary, no *post-mortem* examination was made, but she had exhibited some symptoms of tuberculosis. Her only child died in my wards from tuberculous tumour of the cerebellum. In none of the fatal cases of Graves's disease, though they had been long in hospital, were there any signs of tuberculosis. It may be worth while to direct attention to this fact, and possibly to try the effects of thyroid extract in phthisis; but I cannot say that I am very hopeful of favourable results. Tubercle in the thyroid has not often been observed in ordinary cases, but I have found it in cases of rapid tuberculosis as in a specimen which I show, but I do not think it has ever been seen in myxœdema.

ACTION OF THYROID SECRETION.

Whatever other functions may be subserved by the thyroid in the animal economy, whether in blood formation, proteid metabolism, or as supplementing the action of other organs, we cannot now doubt that all its more important functions are due to a secretion, which can be separated, though not as yet in a pure state. This is abundantly shown by the fact that the symptoms and deleterious results of atrophy, congenital deficiency, or removal can be averted or cured by a substance chemically separated, and introduced by the stomach. This fact, if it threw no other light on the physiology of the thyroid, serves to abolish all the theories grounded on the view that it acts by the removal of a poisonous substance from the blood, or by transforming mucin into "colloid" within the gland. True, it does not prove that no such action is exerted by the substance within the blood or tissues, but it minimises the previous observations as to the accumulation of mucin, etc., in the blood as explaining any part of the pathology of myxœdema. And if, as seems probable, the essential constituent of the secretion should prove to be of the nature of a ferment, the usefulness of the colloid material will also be negatived.

I have recently made numerous observations on the nature of the substances contained in thyroid extracts. But since others more competent are engaged in the work, I need only refer you to such papers as that of Mr. E. White.⁹ No one can, after such observations, question that the amount of the active ingredient forms a very minute proportion of the extract from the gland. The physiological action of the secretion on healthy animals, and to various diseases, also urgently demands further investigation.

The observations on myxœdema can, of course, only be accepted with some deductions. Where only a moderate dose has been employed, the effects of restoration of the normal conditions as to temperature, skin excretion, action of the kidneys, restoration of the general nutrition, and of the cerebral functions, are well known. Valuable evidence is also given by the effects of overdoses, where the rise of temperature is beyond normal, the acceleration of the pulse and its characters, and the production of sweating, diarrhoea, etc., correspond with the phenomena of Graves's disease in many respects. A few observations are also recorded by medical men on themselves. Such are those of Dr. Alex. Haig¹⁰, who found that relaxation of the arterioles, diuresis, etc., were produced by it.

The only satisfactory observation I have made on a healthy subject was one in which dried tabloids were given; the effect was slight irregular rise of temperature, tachycardia. It was noted that the tachycardia and ready excitability persisted for some days after the drug was stopped. The glycerine extract had proved inert in this and other cases.

We cannot but be impressed by the fact that the partial arrest of the several functions in athyrea is removed by thyroid secretion, and may be exaggerated by an overdose.

One is indeed inclined to think that the evidence in this respect is conclusive as to the physiological effects of the secretion.

At the same time one cannot but see that there are flaws in the argument from a strictly scientific point of view, and that it does not serve as proof that a mere excess of the secretion is the sole and essential factor in Graves's disease.

Nor does it seem to me that experiments on the healthy human subject can rightly be made to afford conclusive evidence. For in order to produce all the phenomena we must push the administration to a degree which would be dangerous, and which might lead to permanent damage to the nervous centres and to the heart.

For this reason experiments on animals are essential. In them the doses given might be of such amount and duration as to cause changes in the central nervous system which could be studied microscopically, and might reveal similar changes to those which I have described.

There is one point of especial importance in respect to experiments on healthy animals. In relation to all active secretions there are means by which either the production is controlled or the excess removed. In prolonged athyrea the control is removed, and probably, as in all functional abeyance, the controlling mechanism becomes defective and its agents atrophied. Hence we should expect that the effects of artificially introduced secretion would be more intense than in healthy animals. After partial recovery the control is probably regained.

But in healthy animals, unless this control system is paralysed, the effects cannot be expected to be so great. We do not know, and can only infer, wherein this control lies, and in the human subject, we might find that unexpectedly serious results might follow if disease of the necessary organs existed.

It seems probable that the skin, mucous membrane of the alimentary canal and possibly the kidneys, are the organs of its excretion.

NOTES AND REFERENCES.

¹ Birch-Hirschfeld; also "Die Anschwellung der Schilddrüse bei der Basedow'schen Krankheit beruht wesentlich auf Erweiterung der Gefässe," 3rd edition, 1887, p. 335. ² Dr. Murray (BRITISH MEDICAL JOURNAL) has been misled by an erroneous and unauthorised report. What I said was that there was an enormous diminution (not increase) in the colloid material. ³ Similar observations are common to most writers on the subject, from Graves onwards. Especially frequent is the mention of palpitation and tachycardia, without other symptoms, in cases of enlargement of the thyroid. See Trousseau, etc. ⁴ See especially a recent article by J. J. Putnam on "Feeding Thyroids in Myxœdema" (*Amer. Journ. of Med. Sciences*, August, 1893.) I should have entered more fully into some of his arguments but that I have been only able to see the article since the greater part of this lecture was written. ⁵ Th. Wette, *Archiv f. klin. Chirurgie*, 1892, pp. 652 and 785. ⁶ For example, Professor Grainger Stewart and Dr. George Gibson have recorded two cases in which similar changes were present. British Medical Association, August, 1893. ⁷ See also Putnam, *loc. cit.*, Möbius. ⁸ For an able summary of this question see Ballet, *Revue de Médecine*, 1888, p. 513. ⁹ "The Pharmacy of the Thyroid Gland," *Pharmaceutical Journal*, September 2nd, 1893. ¹⁰ BRITISH MEDICAL JOURNAL, September 23rd, 1893, p. 674. See also Dr. Johnston and Dr. Murray.

PASTEURISM IN COCHIN CHINA.—The statistics of antirabic vaccinations performed at Saigon from May 1st, 1892, to May 1st, 1893, by Drs. A. Calmette and J. Pineau, show that during the twelve months in question (being the second year that the Bacteriological Institute of Saigon has been at work), the total number of persons treated was 62. Of these, 10 (all Europeans) came from the Dutch Indies, 31 (including 2 Europeans) from Cochin China, 14 (including 3 Europeans) from Annam and Tonquin, 1 (European) from China, 1 (European) from Hong Kong, 3 (including 1 European) from Siam, and 2 (both Europeans) from British India. In 12 of these cases it was proved experimentally that the animal which inflicted the bite was rabid; in the other cases the diagnosis of rabies was made clinically on the authority of veterinarians, or in some cases, apparently, of the civil and military authorities! Only 1 of the 62 patients treated died of hydrophobia. This was a Dutchman from Java, who came under treatment only on the thirtieth day after being bitten on the hand; he underwent a complete course of intensive treatment, and died eleven days after leaving Saigon. The bites were inflicted by dogs in all the cases except 1, when the biter was a man suffering from hydrophobia. Since the establishment of the institute, on April 15th, 1891, up to May 1st, 1893, the total number of persons treated has been 110, with 2 deaths, a mortality of 1.8 per cent.