AN ADDRESS ON THE PHYSIOLOGY AND PATHOLOGY OF THE THYROID GLAND.

[WITH PLATE OF MICROPHOTOGRAPHS.]

Delivered before the Medical Society of London.

By VICTOR HORSLEY, M.B., F.R.S., F.R.C.S.,
Surgeon to University College Hospital and to the National Hospital for
the Paralysed and Epileptic.

I TAKE it that what ought to be the substance of what I say to-night is the relationship of scientific laboratory investigation to the progress and improvement of therapeutics. This, however, if treated with severe accuracy, would practically amount to a recapitulation of historical facts which are in the main very familiar to you. I do not therefore propose to expend more than a short period of the hour allotted to me in touching upon old ground, but I desire to lay before you some conclusions derived from observations which I made in 1884-85-86, but have withheld from publication until now, for the reason that so many side issues came in from the original facts and required collateral investigation that I confess I was tempted to put the points aside in favour of more easily attainable knowledge, and which, at least in the case of cerebral localisation, proved of somewhat more immediate value. Moreover, inasmuch as I published in Virchow's *Festschrift*, 1891, an historical summary of the investigations which have led to the greater elucidation of the functions of the thyroid gland up to that date, I may be excused dealing at length with the history previous to 1891.

Nearly one hundred years ago, King, of Guy's Hospital, showed by direct experiment that the colloid material of the acini of the gland passed into the lymphatics, and thus for the first time was suggested in a tangible form the modern view of the so-called internal secretion of the thyroid gland. During the subsequent fifty years, and at a time when, with the exception of snake poison, no animal fluid was known to have a very powerful influence on the body when administered in extremely small doses, it is not surprising that the idea that the thyroid gland had any importance at all in the economy was scouted, and that very absurd opinions were formulated to explain its existence and presence in the neck.

The first great step from this state of disregard was the discovery by Schiff in 1859 that the organ was important to life; but unfortunately his experiments attracted no attention, and as they were performed with a different object than the direct investigation of the function of the organ, the result was obscured.

However, the question was reopened by Schiff scientifically in 1884, and then placed upon an accurate basis, since he definitely proved for the first time that the removal of the organ alone was attended in the carnivora by striking symptoms preceding a fatal termination. At the same time Reverdin and Kocher had established the fact that total removal of goitres was liable to be followed by certain symptoms which, from the description, were recognised by Semon to be analogous to myxœdema; and it was on Semon drawing attention to this matter, that the Committee of the Clinical Society was appointed for the purpose of collecting what information was in existence relative to the disease myxœdema, which had been for some time well recognised in this country.

Up to this point, however, the final proof was wanting that the fatal symptoms of thyroid extirpation were due to the actual loss of the thyroid gland, and no proof existed of the loss of the gland being the cause of myxœdema and cretinism. The reason was that the experiments so far had been conducted for the most part on carnivorous animals, in which the gland is of such essential importance to life that removal of it is followed by an extremely acute cachexia, customarily fatal in a very few days. Such a class of animals consequently did not afford means for the determination of the rôle played by the gland in a disease which runs such an extremely chronic course as that of myxœdema. To really test the question, therefore, attention had to be turned to

the possibility of removing the thyroid gland in classes of animals in which the progress of the malady might be supposed to be slower. It was for this reason I undertook an experimental investigation into the question, employing monkeys for this purpose, and later herbivorous animals, strictly speaking.

The result was to establish beyond question the fact that the typical symptoms of myxœdema could be produced in a monkey by simple removal of the thyroid gland, and the synchronous examination of the other structures of the neck—for example, the nerves, proved also that no injury was done to them, and that therefore the symptoms were solely and wholly due to the loss of the gland itself. In speaking of this fundamental position, it was forcibly brought to my notice in 1884 how a medical theory of the explanation of disease may survive without any basis whatever for nearly a century.

On the first occasion on which I showed at a meeting of the Pathological Society one of the monkeys which had died from myxœdema, thus produced, a distinguished pathologist took great exception to my assertions that the symptoms were due to the loss of the gland, and stated that in his opinion myxœdema was due to changes in the sympathetic nerve.

Now this was really an evidence that the sympathetic theory of disease which Abernethy was at such pains to establish against the experimental methods of John Hunter, was still prevalent in the minds of many; and more than that, when my observations were severely attacked by Professor Munk, in Berlin, it was wholly upon the assumption that the sympathetic and other nerves in the neck had been injured during the operation of ablation of the glands. Of course, as a matter of fact, Schiff had already shown in the carnivorous animal that in that class at least the fulminating symptoms observed were not due to injury of any nerve in the neck, and I also naturally examined both the sympathetic and vagus trunks in the monkeys operated upon, and with wholly negative results.

It is very difficult to understand how such a theory as that of the influence of the sympathetic nerve and its supposed ability to produce constitutional disease can ever have found a serious position in medical literature and work.

Long after it was started the discovery of the influence of the vasomotor system was additionally invoked to explain obscure general symptoms like those of myxœdema, and there was of course some basis for such an opinion in view of the fact that so many of the vasomotor fibres run in the sympathetic trunk, but the fact always seemed to have been lost sight of that in a general constitutional affection there must be some profound chemical change, and while we must be ready to admit that the chemical changes of the body are greatly under the influence of the nervous system, still it will always remain an inexplicable absurdity that one set of nerve fibres should have ever been accredited with the power of producing a widespread disturbance of metabolism.

Of the general character of the athyroidal state, few proofs are more striking than the researches of Hoffmeister and v. Eiselsberg in producing artificial cretinism in young animals by excising the thyroid directly after birth. These photographs show the animals and the changes in the epiphyseal ends of their bones, which latter led to the mischief being termed by Eberth and others "fœtal rickets." But final destruction of the sympathetic theory has now been given by the brilliant discovery of Dr. George Murray that the terrible and fatal symptoms which, chiefly by the clinical researches of Dr. Ord, we are all so familiar with, can be dissipated by the internal administration of that structure the loss of which had caused the disease. We will now commence the discussion of the special points in the functional activity of the thyroid gland, to which I wish to draw your attention to-night.

Since 1891 the microscopic morphology of the thyroid gland has undergone much and interesting extension. The experimental researches of Gley have attracted renewed attention to the organs originally discovered by Sandstrom, and independently observed by Baber, and the existence of which has been subsequently confirmed by a large number of observers, from myself in 1884 to Kohn in 1895.

The relation of the parathyroid to the lateral lobe of the

thyroid has been shown by Prenant to be in the sheep's embryo a distinct outgrowth of the wall of the thyroid vesicular entodermal prolongation. In Prenant's figure it is plain that the parathyroid develops in chronological advance of the thyroid itself, and by reason of its position lies near the hilum of the lateral lobe. At the same age of development must be noted also the proximity of the upper part of the thymus.

The involvement of the parathyroid in the thyroid of a carnivorous animal has been investigated most recently by Kohn, and he describes two masses of parathyroid tissue as external and internal gland, one in the hilum, the other at the opposite or outer surface.

In this macroscopic dissection of the neck of a cat killed by bleeding, the external parathyroid is well seen on the surface, and in these sections from the dog both external and internal masses are obvious (see the microphotograph, Fig. 1).

The structure of the parathyroid has always been looked upon as embryonic thyroid tissue, but, in addition to the point just mentioned of its early development, it needs to be pointed out that it resembles the suprarenal body and the carotid gland so-called, which must be looked upon as adult tissues.

In structure it seems to be made up of columns of entodermal epithelium cells separated by capillaries, and in places the groupings of the columns of cells around a capillary suggest the grouping observed by Arnold in the suprarenal body, and held by him to be characteristic of a glandular and secretory mechanism. This I found in 1885 and 1886 to be specially observable in the parathyroid in cases of compensatory hypertrophy in dogs, but, as Edmunds has shown in his recent valuable paper, no true acini are found and no colloid secretion collected. The gross enlargement of the parathyroid in compensatory enlargement hypertrophy observed by me has been confirmed by Edmunds, and is shown in these microphotographs.

As regards the minuter structure of the parathyroid, the accompanying illustrations exhibit the features dwelt upon chiefly by D. Sandström, Kohn, and Edmunds. In the monkey the capillaries are numerous and often dilated, the cells small, and packed together, but a more interesting point is the similarity demonstrated by Wolfier and Edmunds between embryonic thyroid or adult parathyroid tissue and the tissue of many so-called adenomatous goitres. Contrast these photographs from specimens from the cat and from an adenoma removed by operation, and which last is shown in the microphotograph, Fig. 2.

A word with regard to the vascular supply of the parathyroid. A beautiful injected specimen, for which I have to thank Dr. Gustav Mann, of Oxford, affords the opportunity of comparing the vessels in the thyroid, parathyroid, and a lymph gland in the cat. The relative diminishing vascularity is well marked and the vessels perpendicularly arranged at the margin of the parathyroid clearly exhibited as in the suprarenal body. In the two further photographs illustrative of the vascular secretory apparatus of the thyroid (Microphotograph 3, transmitted light) Dr. Worrall has succeeded in obtaining a striking picture of even the opaquely-injected vessels of the thyroid gland as seen by reflected light. There is, therefore, on consideration of the anatomical facts of the normal and hypertrophied parathyroid gland structure, enough to suggest a basis for confirmation of the position first established by Gley by physiological experiment, namely, that the parathyroid is a gland *sui generis*, and has a specific function related to that of the thyroid gland.

There is a further point concerning the morphology of the thyroid gland worth a moment's notice. In 1884 I drew attention to the existence of tissue resembling lymphoid tissue in the thyroid gland, and suggested that it might have some relation to the anæmia observed to be produced by removal of the gland, and that therefore the influence of the organ in hæmopoiesis might be direct as well as indirect. Exception was taken to my statements, but they have been now fully confirmed, both by Kohn and Abram, as is shown in these photographs.

Kohn in fact, adopting the line taken by Prenant, calls the adenoid tissue the inner thymus, but the exact relations of this to the other portions of thymus tissue in the neck,

notably that on the outer and anterior aspect of the carotid artery, has yet to be determined.

Now that we know for certain that the thyroid gland is a secreting gland which has a very important relation to the metabolism of the body, we can re-examine the epithelium of the acini with a fresh interest. I will first direct your attention to the compensatory hypertrophy of one lobe when the other has been removed, a hypertrophy which both Wagner and myself independently have shown in the dog and cat is a true compensatory hypertrophy. The most remarkable changes are to be observed in the epithelium of the acini as well as in the nature of the contents of these cavities. Further the normal epithelium of the acini, the groundwork of the study of which was first laid in this country by Dr. Cresswell Baber's well-known monographs, and its behaviour when both lobes of the gland or only a part are in full functional activity, has been the subject of special study in relation to the problems of secretion by Langendorff, Hurthle, Neumeister, Anderson.

Langendorff pointed out that the well-known cubical epithelium consists of cells of two distinct kinds, which have a different staining reaction, and one of which appears to have characters suggesting the formation of the colloid material within the cell.

If we first turn to the compensatory hypertrophy, we learn a number of striking facts, and the first change to be noted is that the epithelium alters, and instead of remaining cubical, the individual cells tend to grow out and become columnar (microphotographs, Figs. 4 and 6). In the second place, the outline of the acinus alters; instead of being a more or less rounded cavity, it becomes a cavity resembling the branching of an ordinary gland; in short, it is rather more a conglomeration of tubules than a collection of cystic spaces (microphotographs, Figs. 5 and 6).

This metamorphosis of the ordinary acinus proceeds so far, that in a well-marked case the lumina of the acini are greatly encroached upon, and in many cases are obliterated by the taller epithelium of the two sides coming into contact. Finally, the secretion of the acini, from presenting the appearance of ordinary coagulated but semitranslucent proteid, becomes replaced by less solid—that is, more watery—contents, and ultimately its solid constituents are represented by a granular *débris*, and the original colloid material disappears.

All these changes are shown in the accompanying photographs. This compensatory hypertrophy will be recognised to be parallel to what we observe clinically in a human being under circumstances of parenchymatous enlargement, thus in the so-called parenchymatous goitre the acini are not enlarged, but their outlines become irregular, and the epithelium increases in height. But the most remarkable similarity, and one I drew attention to in 1884¹ in the conditions I observed in hypertrophy was that seen in exophthalmic goitre.

In exophthalmic goitre the acini become more irregular and more resemble a racemose gland, the colloid material tends to disappear, and is represented by a granular *débris*. This is coupled with a general enlargement of the whole gland, just as in the artificial hypertrophic compensation. In the extreme case of which I show you specimens the secretion was a thin watery fluid. Gradual disappearance of the colloidal material is well shown by comparing Microphotographs 7, 8, 9, 10. It is hardly possible to leave the point of exophthalmic goitre without a few further observations. On the question of the symptomatology of exophthalmic goitre I showed in 1884 that the tremor present in all forms of thyroidal lesions was exactly the same as the tremor of acute cachexia strumipriva of thyroidectomised animals, and the fact was subsequently recognised by Charcot and Marie. But the problem of chief moment in the pathology of exophthalmic goitre is the question whether the anatomical changes we have just seen have a causal influence or are only a secondary consequence of some central nerve lesion. As yet the nerve supply of the gland shown in these photographs has not been demonstrated physiologically (that is, by excitation, etc.—Hurthle, self) to exert secretory influence comparable to the well-known effects on the salivary glands. The question has therefore been approached from a clinical standpoint, and in the suggestive papers by Maude and by Abram

¹ Brown Lectures.

Fig. 1.—Sections of entire thyroid of dog. The darkly-stained lateral masses are the parathyroids.

Fig. 2.—Adenoma, resembling parathyroid tissue.

Fig. 3.—Injected thyroid.

Fig. 4.—Commencing compensatory hypertrophy

Fig. 5.—Compensating hypertrophy. (Low power.)

Fig. 6.—Compensating hypertrophy. (High power.)

Fig. 7.—Normal thyroid. (Cf. Figs 8, 9, 10.)

Fig. 8.—Commencing disappearance of colloid material, and proliferation of epithelium.

Fig. 9.—Exophthalmic goitre. (Low power.) Conversion of contents of acini into watery fluid.

Fig. 10.—Exophthalmic goitre. (High power.)

Fig. 11.—The cross is placed immediately below a fat cell, the nucleus of which is vacuolated. Many other nuclei in the preparation can be seen with a lens to be vacuolated.

Fig. 12.

we have a reflection of the recent tendency to regard the symptoms as being due to perversion of the secretion of the gland, the changes in which therefore come to have a primary significance. It is plain that the symptoms are also explicable as being athyroidal, and I venture to suggest that where there is extensive perversion of secretion, that so in proportion there must be a certain degree of athyroidism. Take a single symptom such as the characteristic dyspnoea; that again is exactly the most prominent symptom of the acute athyroidal cachexia in all kinds of animals. Coupled with the dyspnoea is not infrequently a rise in temperature, and in cases where death has rapidly supervened after removal of one portion of an exophthalmic goitre, the temperature may rise to 105° or higher, and the patient die with marked dyspnoea, although of course there is no mechanical interference with the air passages.

I have quite recently had the misfortune, at University College Hospital, of seeing the same condition occur in a patient who was the subject of a very large parenchymatous goitre affecting the whole gland. The dyspnoea was considered to be due to the flattening of the trachea from the pressure of so large a tumour, and though the flattening was found at the operation, I regret to say it did not occur to me that the severity of the dyspnoea might have been in part due to the patient having been in a certain stage of athyroidal cachexia which had been brought about by the involvement of the whole organ in the disease change. Removal of the tumour, although in this case particularly easily accomplished, did not terminate the dyspnoea to which the patient succumbed. At the necropsy the two-thirds of the left lateral lobe left behind for carrying on the function of the gland were found to be extensively goitrous. In future I shall treat such patients with thyroid prior to undertaking the operation.

We may now return to the secretory epithelium, and the colloidal and other products of its secretory activity. Very interesting and valuable observations on this point have been made by Anderson and others who, following on the line initiated by von Wyss, have administered pilocarpin with the effect of obtaining heightened secretory activity on the part of the epithelium.

As regards the changes in the epithelium a great deal has been said by many observers as to the vacuolation of the epithelium and the appearances of vacuolation in the colloidal substance. In the most recent work on this subject—that by Anderson—these vacuoles containing secretion are supposed by him to move out from the epithelial cells and to migrate into the centre of the acinus. It seems unnecessary to do more than remark on this point that the secretion is supposed by many to collect as watery droplets, which naturally appear as vacuoles in the substance of the gland, and of course such secretion is simply extruded from the secreting cell, therefore the view of Anderson is so far coincident with prevailing views. In speaking of the question of the vacuolation of cells, especially in relation to the thyroid gland, I wish to draw attention to the vacuolation, not of the mere protoplasm of the fat cells in myxœdema (Microphotograph 11), which is in itself a common—in fact regular—state of things, but to the vacuolation of the nuclei of the fat cells, and which I believed to be a fairly constant phenomenon in myxœdema. I first observed it in 1885, but could not find any reference in the literature of that time to the matter, and subsequently Professor Boyce and Mr. Beadles independently observed the fact in a case of myxœdema published by them in 1894. Such vacuolation is well shown in these photographs of myxœdematous subcutaneous fat. Since then the question of the vacuolation of the nuclei of fat cells in general has been very thoroughly investigated by Sack, who goes much further and finds that vacuolation of the nuclei of fat cells occurs not only in diseased tissues, namely, lipomata, but also in normal developing fat and in fat undergoing senile degeneration. It is obvious, therefore, that vacuolation of the nuclei of the fat cells, although a very interesting biological condition, is not peculiar to myxœdema, and consequently cannot be regarded as pathognomonic of that disease change.

This photograph from Sack's monograph shows vacuolation of the nuclei not only of the subcutaneous fat in man, but also of the fat cells in marrow, and finally also in large nuclei of the salamander. The so-called vacuoles in the colloid sub-

stance I have referred to, and must now illustrate more fully, are of far less biological interest and significance. As these photographs show, they can be observed in all possible conditions of the epithelium, provided that the latter is capable of forming a colloidal secretion at all. Starting with a pilocarpin result by Anderson, we see actually in vacuolated spaces in the deeply stained colloid material shed epithelial cells containing droplets and granules of colloidal secretion. In this section of an adenoma removed by opening a large vacuole, the secretion contains numerous droplets of a different chemical constitution.

In another you see solid and granular secretion in neighbouring acini, and in another in even the same acinus. In another adenoma with flattened epithelium the colloid is little different as regards degree of vacuolation from this photograph by Hurthle, where the epithelium is heaped up (microphotograph, Fig. 12).

In conclusion, I wish for the opportunity of saying a further word on the retrogression of thyroïdal epithelium. In myxœdema, as is now well known, the thyroid gland atrophies, and there is found a round-celled infiltration of the remnants of the lobes and acini. A photograph taken from a patient who died from myxœdema nine years ago, and a photograph of Mr. Lapidge's drawing of another section from the same specimen, show that in retrogression the cells resemble more particularly the parenchyma cells of Baber; that they are polyangular, and that they occupy the lumen of the shrunken acinus, in which there is consequently no secretion; but it is to be observed that this confirms the importance of the morphological change in the epithelial cell. By way of contrast compare the myxœdematous retrograde cell with that of the compensating active transplanted thyroid in one of v. Eiselberg's striking experiments. In this last there is no colloid, and the secretion must have been a watery one, yet adequate. Estimation of the athyroidal condition, therefore, is rather to be looked for as yet in the changes in the epithelium itself than in the products of its secretory activity.

To summarise our present position and knowledge of the whole question, it is, I think, now generally agreed (and the more so since the recent extensive researches of Mr. Edmunds) that whereas myxœdema and cretinism result from simple loss of the function of the thyroid gland, exophthalmic goitre in its various degrees results from a perversion of that function.

REMARKS

ON

THE EFFECTS OF ANHELONIUM LEWINII (THE MESCAL BUTTON).¹

By S. WEIR MITCHELL, M.D., LL.D. EDIN.,

Honorary Member British Medical Association; Honorary Fellow of the Royal Medical and Chirurgical Society.

THE history of the use of mescal by the Indians of New Mexico is very well known in the United States, and especially through the valuable papers of Dr. Prentiss, of Washington, D.C.²

These so interested me that I asked him to favour me with some of the extract. Profiting by his kindness, I made a trial of the drug on May 24th, 1896, by taking it as I shall now relate.

At 12 noon of a busy morning I took fully 1½ drachm of an extract of which each drachm represented one mescal button. I had in a half-hour a sense of great gastric discomfort, and later of distension. At 1 P.M. I took a little over a drachm. Between 2 and 3 P.M. I noted my face as flushed; the pupils were dilated midway, the pulse 80 and strong. I had a slight sense of exhilaration, a tendency to talk, and now and then I misplaced a word. The knee jerk and station were normal. Between 2 and 4 o'clock I had outside of my house two consultations, and saw several patients. I observed that with a pleasing sense of languor there was an unusual

¹ Read before the American Neurological Society.

² *Therapeutic Gazette*, September, 1895.