THE BROWN LECTURES ON PATHOLOGY.

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LECTURE II.—THE THYROID GLAND: ITS RELATION TO THE PATHOLOGY OF MYXŒDEMA AND CRETINISM, TO THE QUESTION OF THE SURGICAL TREATMENT OF GOÏTRE, AND TO THE GENERAL NUTRITION OF THE BODY (*continued*).

IN my first lecture, I gave a picture of the clinical appearances produced simply and solely by the operation of thyroidectomy. I must now briefly describe the *post mortem* changes, as they are found after death, whether natural, or accelerated a few hours by bleeding. And, in so doing, permit me to draw your attention to the striking resemblance between them and those first described by Dr. Ord.

Rigor mortis appears at about the usual time, and persists normally.

On turning back the skin in an animal that has lived more than one month after the operation, the subcutaneous connective tissue is found to be notably altered. It is swollen, jelly-like, bright and shining, and excessively sticky; the latter quality is most unmistakable. I have made many hundred *post mortem* examinations in man and the lower animals, and do not remember having met with this condition before.

The increase of the connective tissue is most marked in the triangles of the neck, and over the hypochondria. In one case it was continued into the muscles, so as to be obvious to the naked eye, and in this instance (the only one) the muscle contained a trace of mucin. In opening the cavities of the body, the same thing is observed in the loose tissue of the mediastinum and in the omentum; also especially along the coronary arteries and auriculo-ventricular groove. With regard to the distribution of fat in the increased tissue, it is, as a rule, atrophic; in some cases it has completely disappeared from the grooves of the heart, producing exactly the same appearance as may be seen in children who have suffered from a prolonged wasting disease. In one case, in which it was not all gone, it was of a deep orange-colour, and under the microscope it could be seen that the oil-droplet in almost every vesicle (every one in the bone-marrow) was breaking up into several major portions and innumerable small droplets crowding the protoplasm of the fat-cell. Clearly these were atrophic changes.

In the fat which normally should occupy the auriculo-ventricular grooves and accompany the coronary arteries, the appearances of atrophy are most striking, as seen in the microscopic specimens before you; namely, removal of the fat and wasting and disappearance of the fat-cell; and the result is that we have left merely the connective tissue skeleton of each lobule, with its wonderfully rich network of capillary vessels, forming a convoluted mass.

The changes in the connective tissues may, therefore, be summed up as hypertrophy of the fibrous elements, coupled with mucoid transformation of the ground-substance, and, at the same time, atrophy of the fat.

The *serous membranes* have been incidentally referred to.

I have never observed any change in the *bursa*, but, in two cases, have found congestion of the synovial membrane in the *larger joints*, but no effusion into the same.

The *bones and cartilages* appeared unaltered to the naked eye, as also the marrow, which, as a rule, showed numerous leucocytes, containing hæmoglobin; but in one case these were rare, and in the gelatinous marrow, from a dorsal vertebra of the same animal, there were corpuscles of a distinctly myxomatous or mucoid appearance.

Although the *muscles* were the seat of the active tremors described, as yet nothing more than increase of connective tissue has been observed in them.

The organs of the *circulatory system* partake of the general changes so obvious in the connective tissues and in the sections of the heart exhibited; the changes in the connective tissue surrounding it, referred to above, are well seen.

The *respiratory organs* appeared perfectly normal, except in one case, where there was distinct oedema of the middle lobes of the lung.

The *alimentary canal*, naturally the large mucin-secreting surface of the body, as has already been shown, undergoes extensive change, and the parotid and submaxillary glands are found, *post mortem*, to be considerably increased—three to four times the normal size; the swelling consisting of a semitranslucent pale enlargement of all the

lobules of the gland. From the cut surface a sticky glairy fluid exudes, quite the reverse of the healthy secretion. This is, of course, most striking in the parotid gland, which normally secretes a watery serous saliva, but in this case has, as it were, been pressed into the service of excreting mucin. In the instance of the submaxillary gland, we have rather an exaggeration of a more or less normal state of things. Microscopically, this is definitely proved. The parotid cells are swollen by mucinogen, or a substance closely resembling it, and, in extreme cases, are destroyed, in a way similar to the destruction (temporary, it may be) of the intestinal goblet-cell.

This extraordinary, and, so far as I know, novel state of things, is fully borne out by Dr. Halliburton's chemical analysis of the organs in question. You will see from this table that, whereas from the

Table of Analysis of the Tissues showing the Amount of Mucin before and after Thyroidectomy.—By W. D. HALLIBURTON, M.D.

	Skin, Subcut. Tissues.	Tendon.	Muscle.	Parotid Gland.	Submaxillary Gland.	Blood.
I. Normal.						
Monkey No. 1c	.89	.39	0	—	—	0
" " 9	.9	.5	0	0	.01	0
II. Abnormal after Thyroidectomy.						
No. 1 lived 55 days	3.12	2.55	0	.72	6.0	.35
" 3 " 32 "	—	—	—	—	—	Trace
" 5 " 49 "	2.3	2.4	Trace.	1.7	3.3	0.8
" 10 " 7 "	.45	.904	0	Trace	.16	Very small trace.

normal parotid no mucin could be obtained, in the myxœdematous gland an average quantity of 1.21 per 1000 was found; and, for the submaxillary, the numbers are, .01 per 1000 for the normal, and 4.6 per 1000 for the diseased condition. So you see there is an enormous increase of mucin in these organs, as the result of extirpation of the thyroid gland. To put it more clearly, perhaps it would be better to say that the increase of mucin in the connective tissue generally over the body is three to four times the normal amount, but in the parotid it is one hundred and seventy times at least.

The mucous membrane of the whole intestinal tract appeared swollen in three cases, and in all it had a semitranslucent appearance; but there was observed four times an exaggerated secretion of mucus in the excreta from the bowel, in one case the mucus forming tenacious strings.

So much has been made of the swelling of the tongue in human myxœdema, that I must briefly notice its condition in the artificial affection. In the monkey, this organ is normally of large size, and occupies the greater part of the mouth-cavity. It is, therefore, difficult to say whether it is swollen or not; but I am inclined to think it is, since its outline is much rounder and fuller than in a healthy animal.

Perhaps the most interesting change in the abdominal organs is the swelling of the spleen. This, *post mortem*, is found to be hypertrophy of the whole organ, which is simply increased in size, and of a perfectly normal appearance.

The remaining abdominal viscera show little change beyond pallor.

Considering the profound nature of the nerve-symptoms, it might be expected that considerable changes would be found in the *central nervous system*; but, as a matter of fact, the naked-eye appearances of such change are simply those of anæmia and atrophy. The brain and spinal cord are very pale, and the sulci of the cortex cerebri are deeply marked, the meshes of the pia mater being distended with fluid. In short, there is some wasting of the convolutions.

Owing to the short interval of time that has elapsed since the death of those animals which showed most marked symptoms, it has not been possible to prepare sections of the tissues; consequently, I must leave this point undecided as regards the nerve-centres. But you will see that in one case, in which the symptoms were extremely marked, the animal dying in a week, there are no very obvious changes.

The *peripheral nervous system* shows no change to the naked eye; and, microscopically, both the cervical sympathetic and musculo-spiral nerves are evidently quite normal, as you may see in the specimens exhibited.

The importance of these elementary facts will be obvious directly.

We may sum up, then, this somewhat tedious list of tissue-change

in the following way. Ablation of the thyroid causes atrophic changes in the central nervous system, and in the fat generally. It causes an increase in the general connective tissue, and a mucoid conversion of the ground-substance. This increase of mucin in the connective tissue is accompanied by an extraordinary secretion of the same stuff by means of the salivary glands, and also those of the alimentary canal.

While these changes are being wrought in the skeletal and alimentary structures, the hæmopoietic tissues are found to have undergone an obvious compensatory hypertrophy.

We are now able to review the theories which have been put forward to explain the symptoms of myxœdema, cachexia strumipriva, and cretinism; and first let us show you how, in these diseases, the chief symptoms are exactly like one another as set forth in this table.

Comparison of Symptoms.

	Cretinism.	Myxœdema (Ord).	Cachexia Strumipriva (Köcher).	Cachexia after Thyroid-ectomy
Central Nervous System:				
Intellect: Ideation (1) abstract	Diminished	Diminished	Diminished	
Intellect: Ideation (2) concrete	Tardy cognition	Tardy cognition	Tardy cognition	Tardy cognition
Emotions	Diminished	Diminished	Diminished	Diminished
Motion	Paretic	Paretic	Paretic	Paretic
"	Epileptic	Tremors	Tremors and tetany	Tremors
Sensation	Tardy appreciation	Tardy appreciation	Tardy appreciation	Tardy appreciation
Face	Immobile	Immobile	Immobile	Immobile
"	Broad and thick	Broad and thick	Broad and thick	Broad and thick
Hands and feet	Broad and thick	Broad and thick	Broad and thick	—
"	Cold	Cold	Cold	Cold
Skin and hair	Dry and atrophic	Dry and atrophic	Dry and atrophic	Atrophic
"	Puffy	Puffy	Puffy	Puffy
Blood	—	Oligæmia	Oligæmia	Oligæmia
Urine	Normal	Normal	Normal	Normal
Temperature	Low	Low	Low	Low
Mode of death	—	Coma	Coma	Coma

Cretinism, as is well known, has been attributed to every cause except destruction of the thyroid. Chalky water, damp close air, miasma, insufficient food, etc., and hereditary influence, have all been credited with the power of causing the imbecile condition which is so familiar to everyone. So strongly prevalent was this idea, that the Commission (*Rapport*) instituted in 1845 by the Piedmontese Government came to the conclusion that cretinism and goitre were "essentially distinct," and that "their frequent coexistence in the same locality is due to a simple coincidence." First, it was ably urged by Fodéré (*Traité du Goître et Crétinisme*, Paris, an. iii) that cretinism owes its origin to the same remote cause as goitre; and both Tourdes (*Gazette Hebdomad.*, tome i, p. 784—a review of his work) and himself saw in the heredity of cretinism and goitre a strong proof of this position.

I think it will be scarcely necessary for me to go at greater length into this question, having pointed out the identity of the symptoms; but I must add the conclusions of Baillarger (*Enquête sur le Goître et le Crétinisme, Recueil des Travaux du Comité Consultatif d'Hygiène Publique*, tome ii, 1873) that three-fourths of cretins were goitrous, while the endemic character of the one condition varied with the endemic intensity of the other. Baillarger's facts show most clearly that we have every degree between the two conditions, seeming to indicate that the gradual destruction of the thyroid gland by disease determines the cretinous condition.

It is not necessary for me to quote Dr. Ord's lucid description of myxœdema; but, for comparison, let me show you, on the screen, photographs of a myxœdematous patient, for which I am greatly indebted to Dr. Lunn. It is impossible to adduce stronger evidence on this point than that derived from the study of congenital cretinism, as we find it occurring sporadically in England. Through the great kindness of Dr. Fletcher Beach, of Darenth Asylum, I here show you a photograph of one variety of the affection; namely, that described by Dr. Hilton Fagge, in which condition the thyroid gland is almost invariably absent, or, as in one case, the seat of a new growth. These are the cases in which, although, no doubt, there is a congenital predisposition to the change, the symptoms often appear or are only noticed after birth, and in which general hypertrophy of the connective tissues in the posterior triangle gives rise to the so-called fatty tumours in the neck.

I cannot refer to congenital cretinism without showing you this photograph of a specimen in the Royal College of Surgeons (for leave to exhibit which I am indebted to Mr. Stewart); namely, the truly congenital form which has been described by Dr. Barlow and Mr. Bowlby. So far as I know, none of these infants have been born alive; and in this one, at any rate, there was a well marked thyroid gland; so, whether this be quite of the same nature as those I have been describing, must be left undecided; but I show it here to make the series of possible varieties complete.

Whether the endemic disease of the gland is primarily produced by unwholesome water, food, or air, still remains a mystery, and does not immediately concern us; my only object in giving these details being to show you the strong probability in favour of the cretinous state being dependent upon destruction of the thyroid gland.

From cretinism we will now turn to the remaining conditions in which we know the fact in common to be the total disappearance of the thyroid gland. But, although I lay stress on this point, and hope I have shown evidence in support of its being the true causative influence determining the diseased condition, I shall now proceed to show you that the causation of myxœdema has been attributed to utterly different influences; and the distinguished discoverer of the cachexia strumipriva has published a view of the mechanism of the condition which leaves out of sight the function of the thyroid gland. We will examine these theories in the light of my experiments; for, as I have shown you in full detail, all the pathognomonic signs which I have observed follow directly as the consequence of simple excision of the thyroid gland.

To take the cachexia strumipriva first, Köcher shows that, after total excision of the diseased thyroid, there follow invariably the symptoms of myxœdema, precisely the same as I have described in the first lecture, even including tetany and fibrillations in the muscles; but he argues, with apparent force, that these are the physiological symptoms of chronic asphyxia, due to narrowing of the trachea, consequent on softening and atrophy, produced by ligature of the arteries supplying it, the ligaturing of the vessels being performed at the time of operation; for he has shown by injection, what has really been known many years, that the thyroid arteries supply the trachea and part of the gullet also. A little consideration will make it obvious at once, that this view is completely untenable in the light of innumerable cases in which there exists marked stenosis of the larynx and trachea, but not a symptom of myxœdema. A final proof lies in the fact that I have always found the larynx and trachea absolutely normal and patent; we will, therefore, not consider this further, but pass on at once to the next theory, which originated with Dr. Hadden (*Brain*, vol. v, p. 188, 1882), namely, that the myxœdematous state of malnutrition was brought about by a primary general spasm of the arterioles and capillaries, the spasm being maintained by central disturbance in the sympathetic ganglia, and possibly in the medulla oblongata. This view regards the atrophy of the thyroid body as due to the constriction of the blood-vessels, and, therefore, of secondary importance. Accepting this view as probably the correct one, Köcher and other authors have assumed that, in the operation of thyroid-ectomy, the sympathetic nerves are injured and irritated by being included in the ligatures placed on the vessels. But Schiff (*loc. cit.*) found that, if he exposed the gland and divided the nerves going to it, the symptoms did not follow; although, from his method, there must have been considerable irritation of the nerves. Further, by my method, I fail to see that there was any more than a momentary irritation, as the nerve was divided, and, microscopically, the sympathetic trunk and ganglia appear to be absolutely normal.

I show specimens of sympathetic ganglia from cases of myxœdema, which I owe to the kindness of Dr. Hale White, which certainly indicate an increase of connective tissue; but that may be part of the general increase throughout the body.

As to the medulla oblongata, I can find, microscopically, no change in it as yet, but my observations are not complete on this point.

There remains, then, the theory that these varieties of a general state of malnutrition are due to the loss of function of the thyroid gland.

I have placed this last, as, to my mind, the explanation *par excellence*. And it is gratifying to find that Dr. Ord in his, the first accurate, description of this condition, drew attention to the diminution, indeed destruction, of the thyroid gland.

This very point has been called in question quite lately; and it seems to me that the possibility of our having to deal with varying degrees of this peculiar malnutrition has been entirely overlooked. Further, although a thyroid body may be discovered *post mortem*, it will require a great deal more research before we can admit that it was in full normal function. Here is such a specimen, lately removed

from the patient of whom I just now showed you a photograph. The analysis of his tissues is not complete, but he presented many of the classical symptoms; and a full report of the case will subsequently be given by Dr. Larder.

No one could be prepared to formulate a theory of the full pathology of the conditions I have been describing in the present state of the subject, but certain facts are so striking, that it will, perhaps, aid in further investigation if they are enumerated in a tabular form—first the anatomical, and then the physiological.

1. The thyroid gland appears to consist of two distinct portions; (a) glandular, consisting of highly vascular acini, which excrete into their interior a mucoid substance, this substance, or something closely similar, being found in the lymph-vessels of the gland: mucin-excreting function? (b) highly vascular lymphoid nodules: hæmatogenous function.

2. Excision of the gland is followed, according to my experiments, by an increase in the amount of mucin in the tissues which normally possess it, by a retrograde histological change, by an increase in the activity of the glands which normally secrete it, and (what is still more striking) by the assumption of the muciparous function by a gland which normally produces none, or very little, mucin—by the parotid gland.

3. Excision of the gland is followed by profound changes in the blood, namely, a diminution in the number of corpuscles, preceded, as regards the white elements, by a temporary increase in their number, by an alteration in the coagulability and albumins, and by an abnormal presence of mucin. (The latter facts were discovered in my specimens by Dr. W. D. Halliburton.)

4. Excision of the gland is followed by nerve-symptoms, indicating changes in the lowest motor centres, these changes causing tremors, with rigidity and paresis; it is also followed by changes in the higher psycho-cortical centres, such producing imbecility, and, ultimately, death in the comatose state.

It would obviously be absurd to assert at present any more than that the primary lesion is thus proved to be the loss of the thyroid gland, and that the symptoms are probably directly due to that, even if through the intervention of the nervous system, for I am far from wishing to exclude the possibility of a vaso-motor or trophic change being the immediate cause of the alteration in the connective tissues; but the evidence here collected seems to clearly show that disturbance of the nerve-centres, which leads to such vaso-motor or trophic change, is directly caused by the loss of the thyroid body.

Moreover, in using the expression "loss of the thyroid body," I mean loss of its functional activity; and personally, I believe, in those cases of well marked myxœdema where a thyroid body is found, whether anatomically altered or not, that it is not acting normally. But it is impossible to put out of sight without further reference the formation of a mucinoid body, namely, the acini of the thyroid on the one hand, and the increase of mucin in the tissues after thyroidectomy; and if we find at the same time that the muciparous glands have much increased their action, the question arises whether we have not to do with the simple case of total removal of an excretory organ, with the usual result of death.

This view receives the strongest support from further experiment. If one lobe be excised, the other hypertrophies. If this enlarged half be now removed, the animal presents many of the symptoms described; but Schiff (*loc. cit.*) states that, provided an interval of about three weeks elapses between the operations, the symptoms do not appear, or at any rate are not fatal. It is doubtful whether we can trust this observation, but at any rate we can understand the symptoms being much mitigated, as time will have allowed the spleen to provide for the hæmopoietic function of the gland.

Beyond this, it would be unscientific to speculate further; and, having proved that the thyroid gland is one of the most important structures in the body, I shall conclude the subject by discussing the original object of my research, namely, the proper surgical treatment of goitre.

Putting aside the rare condition of inflammation of the gland, which must be treated on general principles, we find that there are practically three groups of conditions which call for treatment, namely, (1) hypertrophy, or more correctly adenoma, with or without some amount of cystic degeneration and fibroid overgrowth; (2) cystic disease; (3) malignant new growth. As to the last condition, it may be disposed of at once by saying that, whether only palliative or not, total excision is the only treatment.

Hypertrophy or adenoma must necessarily be considered under the two headings of exophthalmic goitre and ordinary goitre. Excision of the tumour, or of part of the tumour, is said to have cured one case of the former, and partial excision is perhaps the only treatment which holds out a possibility of cure.

The operative treatment of ordinary goitre, whether cystic or adenomatous hypertrophy, is summed up most briefly under the headings injection and excision; one or the other of which is rendered imperative by the failure of general treatment, with iodine internally and externally.¹

Injection may be simple, or combined with laceration of the tumour-substance by the point of the needle, as practised first by Billroth; this, however, is so dangerous, by reason of secondary inflammatory consequences, that it should be abandoned.

The danger of simple injection is only one, it is true, but extremely serious, namely, sudden death. This has been usually attributed to the fact of the cannula piercing a large vein, and then the injection of air into it. But it seems to me that practically this can rarely happen, for there are few surgeons who would ever inject fluid into a cavity without, as a matter of routine, expelling the air from the syringe; and, even if this were not done, the available air would be under a cubic inch, considerably less than what Mr. Erichsen's experiments on dogs showed to be necessary to cause death. I believe the real cause of death is the injection of the iodine or ferric chloride solution into one of the enormously large veins, with instant thrombosis of the right side of the heart as a consequence. I here show you the heart of a dog, into the external jugular vein of which (while it was under ether) I injected fifteen cubic centimetres of tincture of iodine. The death from cardiac paralysis was instantaneous, and the reason was obvious on the immediate *post mortem* examination; namely, complete plugging of the right cavities with hard clot, which looked as if it were weeks old, instead of a few seconds. It might be supposed that death followed irritation of the medulla oblongata by the circulation in it of the iodine, but a previous injection of five cubic centimetres had no immediate effect on the respiratory centre, the most delicate in the bulb.

Avoidance of this awful accident would seem to be perfectly easy by following the rule of Demme (Gerhardt's *Handbuch der Kinderkrankheiten*, Art. Krankheiten der Schilddrüse, 1878); namely, to test the possibility of having wounded a vein by waiting after the puncture for a flow of blood to indicate the same before injecting the fluid.

The treatment by excision of the tumour is thus the last and the most important part of the whole subject, as having really aroused a sense of the importance of the thyroid gland.

It will be perfectly obvious from what has been said before, that, under no circumstances, is it justifiable to excise the whole gland for the ordinary adenomatous or firm cystic goitre.

Portions of one lobe, or the whole of one lobe, may be removed, as has often been done with perfect relief to the patient; but there is an operation, introduced into English practice by Mr. Sydney Jones, which appears to combine all possible advantages. I mean excision of the isthmus of the gland itself. In a letter which Mr. Jones kindly wrote me, he states that this simple operation is performed by removing the isthmus between silk-ligatures; and that it is followed invariably by shrinking of the goitre, and no myxœdematous symptoms. This is what might have been expected from *a priori* reasons; and seeing that the operation mechanically liberates the trachea, relieving simply the symptoms of dyspnoea, it appears to me to be so obviously the least objectionable in the view of recent discoveries, as to claim a first trial before the part or whole of one of the lobes is removed.

As regards excision of cysts, there can, of course, be no objection to such treatment, as at the most it only corresponds to the excision of part of a lobe.

Considering the attention now given to the subject of the thyroid body generally, we may hope ere long to find many of the doubtful points solved; but I trust that I have brought before you fair evidence to show that cretinism, true myxœdema, cachexia strumipriva, and the cachexia after thyroidectomy in animals, are simply the symptoms following the loss of the function of the thyroid gland.

¹ In passing, I would note the existence of primary symptoms of myxœdema in patients the subjects of ordinary goitre. In a lady under my care, I have found all the characteristic symptoms enumerated above, which are disappearing as the goitre is diminishing.

SUPERANNUATION.—Mr. George Bland, late medical officer and public vaccinator for the Eastchurch district, and the workhouse of the Sheppey Union, has obtained a superannuation allowance of £50 a year.

BEQUESTS.—Miss Elizabeth Roe has left £500 to the Adelaide Hospital; £200 to the Hospital for Incurables; £200 to the Convalescent Hospital, Stillorgan; £200 to Rathdown Hospital; and £200 to the Stewart Institution for Imbecile Children.