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PATHOLOGY AND TREATMENT OF GRAVES' DISEASE.

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GENTLEMEN,—The investigations and discussions with regard to the pathology and treatment of Graves' disease have reached a point that makes it possible to present several important issues of scientific and practical interest in a moderately definite form.

The essential questions are these: Are the symptoms of Graves' disease mainly toxic in origin, and due to an excessive or perverted secretion from a diseased thyroid gland; or does the affection belong to the class of the so-called neuroses; or, finally, are the symptoms due to an irritation of the thyroidal and cervical nerves?

If it can be determined that the thyroid is directly or indirectly the principal cause of the disease, then a strong case is made out for the removal of that gland by surgical means, provided no strong contra-indications are present. As a matter of fact, this operation has already been done in a large number of cases, and on the whole with encouraging results. The most successful results are, however, as we too well know, liable to be published first, and the proper position of thyroidectomy in the treatment of Graves' disease has yet to be established. My own experience with two cases has made me feel the need of caution in recommending this treatment.

The writer who first called attention to the importance of the thyroidal theory, and who has given it perhaps the strongest support, is Mœbius.[1] Other writers of promi-

[1] Schmidt's *Jahrb.*, vol. ccx., July 15, 1886; *Zeitschr. für Nervenheilk.*, 1891; and other papers.

nence have skilfully maintained the same view, two of the latest of them being Dr. Greenfield, of London, who makes this topic the subject of the Bradshaw lecture of 1893,[1] and Rehn, of Frankfort,[2] who has had much practical experience with the surgical treatment of these cases.

The argument for the thyroidal-secretion theory, drawn from the successful results of operations, is not as convincing as it at first sight seems. It happens often enough that morbid processes are kept up by influences which were not their real cause, and cease when these influences are withdrawn. Furthermore, the symptoms of Graves' disease have sometimes been favourably influenced by such operations as the draining of a cyst of the thyroid (Rehn), or removing a sarcoma (Tillaux) without doing much if anything to the secreting portions of the gland ; and operations for the removal of irritations from the nasal cavity have also been remarkably effective in a few cases in giving the first impulse toward cure.

The thyroidal theory has taken, in general, one of two forms : (*a*) That the amount of the thyroid secretion is increased, and, being poured into the blood, acts as a poison to the nervous system, and perhaps to other tissues ; (*b*) That the thyroid secretion, whether increased or not in quantity, is altered in character (v. Mœbius). The latter view was proposed to meet the objection that some of the symptoms of Graves' disease may appear before any recognisable glandular enlargement has occurred. The idea of an altered secretion is ingenious and suggestive, but is not yet substantiated. A great deal of careful chemical and physiological work must be done before we can decide such a question. Greenfield says that the secretion of the diseased gland is liable to become mucinoid, instead of colloid, in character, but this does not greatly help us. Now that Graves' disease is more commonly treated by thyroidectomy than formerly, it should be possible to obtain fresh material for direct experimentation, but until this has

[1] *Lancet*, December 9, 1893.

[2] *Deutsche med. Wochenschrift*, 1894, p. 265.

been done we ought to admit that we know simply nothing of the action of perverted thyroid secretion. It is difficult to believe that just the same perversion would occur in each case, always giving rise to much the same symptoms, *i.e.*, the symptoms of the typical Graves' disease, and it would not be proper to accept the arguments adduced in favour of the increased secretion theory as necessarily supporting the perverted secretion theory. It has also been suggested as possible (Maude, *Lancet*, 1893), that even when no obvious enlargement of the thyroid has occurred the secretion may be increased in quantity, but before much weight is attached to this view, as yet unverified, the validity of the thyroid theory in general deserves further scrutiny.

(1) It is pointed out that Graves' disease presents various points of similarity or antithesis to the myxœdematous cachexia which follows the removal of the thyroid. Thus, in the first stages of this cachexia, symptoms of nervous excitability make their appearance, which are not unlike some of those characteristic of exophthalmic goitre. The temperature may be elevated, tremors are often present, and muscular jerkings sometimes occurring in broken series.

(2) Besides these points of resemblance, there are also points of contrast which are very marked at first sight—though, perhaps, they are in reality rather superficial—between the symptoms of Graves' disease and those of the later stages of cachexia thyreopriva, or the ordinary condition of a myxœdematous patient. This contrast is tersely expressed by Mœbius,[1] who says : " In the one case we have enlargement, in the other diminution in the size of the thyroid gland ; in the one a rapid, in the other a slow heart beat ; in the one we have a fine skin, warmer than usual and inclined to sweat, while in the other the skin is thick, cold, and dry ; on the one hand we see increased mental irritability, a condition of irritable weakness, on the other slowness and dulness of the mind."

It is certainly obvious that in these two conditions we have symptoms which are in a measure the antithesis of each

[1] *Zeitschr. für Nervenheilkunde*, 1891.

other, but this fact should not be admitted as indicating more than it really does indicate. Many of the strictly nervous symptoms of Graves' disease, such as the tremor, irritability, increased heart beat, and flushing of the skin, are met with in conditions of nervous excitement where no question of increase in the thyroid secretion comes in at all. As regards the differences in the condition of the skin, it is doubtful if there is any real contrast between the state induced by a relaxed vascular contraction and increased activity of the sweat glands, and that due to such manifest structural changes as are seen in myxœdema, where the diminution in perspiration is, for all we know, a secondary element. Fortunately, we have in the extracts of animal thyroids, now so largely in use for myxœdema and other states, a means of studying the action of the thyroid carefully and at leisure.

To some extent this has already been done, and the results seem, in some, though not in all respects, confirmatory of the thyroidal theory of the origin of Graves' disease. These facts have been passed in review by Murray (*Lancet*, London, 1893), Greenfield, and others. An excess of thyroid extract seems to cause, quite regularly, even in healthy persons, to judge from the few experiments reported, an increase in the pulse-rate and temperature, and often diuresis with increased secretion of urea. Myxœdematous patients are sometimes very susceptible to this substance, and sometimes suffer from serious prostration, with anginoid and neuralgic symptoms, as the result of a dose which other patients bear with ease.[1] In such cases, however, important changes in the metabolism partly related to the previous myxœdematous state, are rapidly going on, attended with great loss of weight, and it may be that these changes, or possibly the absorption of toxic products, are in part the cause of the symptoms noted. Loss of weight is, indeed, apt to occur even with healthy persons who are taking thyroid preparations, and yet it is noteworthy that patients with Graves' disease are not especially prone to emaciation as one might expect them to be if poisoned with

[1] See, for example, Shattuck: *Boston Medical and Surgical Journal*, 1894.

thyroid secretion. It is obvious that the absorption of too much secretion or of an altered secretion might cause some of the symptoms of Graves' disease, but it cannot be said that anything like a clear case is made out in favour of the whole complex being due to that cause.

It has been said in this connection that thyroid extracts given to patients with Graves' disease seem as a rule rather to increase than to diminish the symptoms already present, but I do not consider this argument to be of much value. Inasmuch as the thyroid preparations increase the heart-beat in normal persons, it is obvious they would be likely to increase the tachycardia of Graves' disease, but even this is not a regular occurrence. I have been giving of late five to ten grains daily of desiccated thyroid to a patient with Graves' disease without any increase in her palpitation or nervous symptoms, and, in fact, with relief to some of them, and others have had the same experience.

A striking case of this kind has been published by Owen.[1] This physician attempted to treat a case of typical Graves' disease of twenty years' standing by the use of thyroid extracts. The patient's wife, by mistake, administered a quarter of a pound of chopped thyroid on each of two successive days. This was followed by nausea and eructations, vertigo, insomnia, swelling of the face and legs, but nothing of greater import. A week later the treatment was resumed, and a quarter of a lobe of sheep's gland was given daily, as originally ordered. Steady improvement soon began, which progressed so far that the pulse fell from 126 to 76 beats per minute, the exophthalmos almost disappeared, and the patient became able to do heavy work. A single fact like this is of great value, and seems to show that the improvement in the general nutrition which has now been shown to occasionally follow the use of the thyroid in non-myxœdematous cases may sometimes be made to serve a good turn in the treatment of Graves'[2] disease.

[1] *British Medical Journal*, Dec. 2, 1893.

[2] See a paper by the writer in the *Boston Medical and Surgical Journal*, February 15, 1894.

It occurred to me last winter while watching a case of thyroidectomy for Graves' disease,[1] that some of the ill effects of this operation may be due to the pouring out of a large quantity of thyroid secretion from the cut surface of the gland into the fresh wound of the neck. In this case a glairy substance actually exuded into the dressing. If the reports may be trusted these ill effects do not, to be sure, always occur, but in four cases (one of them a case of ordinary goitre) which have come under my observation, the patients were very ill, and the pulse very rapid. One of the patients died at the end of a week, though doing well in all respects except for restlessness, nausea, and cardiac weakness.

(3) Another argument adduced by Greenfield in favour of the thyroidal theory is that the histological examination of the thyroid shows that in Graves' disease we have evidence of an increase of the gland with signs of considerable activity. The thyroid of the adult is made up mainly of small and irregular spaces, lined with epithelium and containing colloid. In Graves' disease the structure becomes arborescent, suggesting that of a secreting gland, the epithelium becomes higher, and the colloid disappears or is changed into a substance of different character.

There is, however, another and quite different significance which may, with quite equal reason, be attached to these changes. It was pointed out several years ago by Halsted and Welch, of John Hopkins' Hospital,[2] that when the thyroid is mutilated, changes similar to those to which Greenfield has referred, regularly occur. In this case we are dealing with a regenerating gland-stump, but Canizzero[3] has found closely similar changes to occur as the result of slight injuries to the gland, such as were induced by separating it carefully from its attachments for the purpose of uniting it to the muscles of the neck. The histological changes occur-

[1] Operation by Dr. J. C. Warren. See a paper by the writer in the *New York Journal of Nervous and Mental Diseases*, December, 1893.

[2] Unpublished communication to the Association of American Physicians; see *Transactions* for 1893.

[3] *Deut. med. Wochenschr.*, 1892, p. 184.

ring under these circumstances are characterised as a reversion towards the embryonic state. Perhaps they indicate an attempt at more active functionating, but more evidence of this is needed than we now possess. It is also noteworthy that even in phthisis changes perhaps analagous may occur.[1]

Again, it sometimes happens that Graves' disease gives place rapidly to myxœdema,[2] and this certainly looks as if the changes in the gland in Graves' disease were of a destructive tendency. Moreover, it is well-known that Graves' disease sometimes occurs gradually as a complication of ordinary goitre, and we have no evidence to show that under these circumstances any further increase in the secretion of the gland goes on.

Furthermore, if we may trust an observation by Sollier,[3] myxœdema, beside its liability to follow Graves' disease, or to occur in some other member of the family of a goitrous patient, may even co-exist in some measure with it.

Yet myxœdema can hardly be supposed to come on while the thyroid is secreting an excess of its active principle.

It is true that some of the symptoms of Graves' disease suggest the presence of some poison, and physiological experiments with the urine of such patients seem to indicate an unusual toxicity,[4] but we know nothing of the origin of this poison, nor whether it is the cause or result of the nerve disease.

It would be difficult to explain, on any toxic theory, the fact that the exophthalmos is usually greater on the side of the larger lobe of the thyroid gland.

Whether the thyroidal theory stands or falls, there is another element in the causation of Graves' disease which is so important that we ought to hold a clear conception of it in our minds. Before speaking of this, however, I shall

[1] Defaucomberge, cited by Horsley, *British Medical Journal*, vol. i., 1892.

[2] See Clinical Society's Report, 1886, and a paper by the writer published in the *American Journal of the Medical Sciences*, September, 1893.

[3] *Rev. de med.*, 1891, p. 1000.

[4] See for example Boinet et Silbert, *Rev. de med.*, 1892, No. 1.

call your attention to a few peculiarities in the history of Graves' disease, and of the patients who are afflicted with it. In the first place, it is admitted that Graves' disease often appears, and often with great suddenness, under the influence of fright or other forms of painful emotion. These are, in fact, its most common exciting causes. It is not, however, generally recognised that the symptoms may also disappear with considerable rapidity, in an acute case, provided the conditions are favourable. Dr. Gowers reports such a case, and my colleague, Dr. F. Coggeshall, has seen a very striking instance. Again, Graves' disease rarely makes its appearance except in neuropathic families. Finally, I wish to point out the very striking fact that Graves' disease may be complicated with any one or more of a variety of other disturbances of the nervous system, and finally of other organs of the body. Such accompaniments are various forms of insanity, diabetes, muscular atrophy, and even myxœdema.[1]

The bond between these two affections may be analagous to the bond which unites Graves' disease to so many other morbid processes; that is, the existence of a neuropathic taint. Generally, to be sure, myxœdema is associated with Graves' disease, and occurs when the destructive processes which occur in the gland have reached a certain point.

There is one important principle which should be kept clearly in sight when we endeavour to trace out the ætiology of an important nervous affection like the one now before us, and this is that the symptom complexes which we see in the disease are often only exaggerations or caricatures of physiological or quasi-physiological arrangements. Thus, there is the physiological provision for rapid action of the heart to meet the needs of sudden exertion. But when this arrangement works, as one might say, too well, *i.e.*, over sensitively, we have morbid forms of palpitation. Similarly, the physiological act of attention in the presence of danger includes fixation, and perhaps even slight protrusion, of the eyeballs, and a general tension of the muscles of the body, and this often passes over into something closely resembling the symp-

[1] Sollier, *Rev. de med.*, 1893.

tom complex of Graves' disease. The fixed muscles begin to tremble, the heart beats come quicker, the breath comes faster, watery discharges may occur, and the whole vasomotor system is liable to be more or less paralysed.

If all cases of Graves' disease originated in fright, we might well assume that the symptoms were due to an overstrain of medullary and other centres intimately related to the emotional centres of the brain. But even for a case not originating in fright this explanation may be made to throw light on the origin of the symptoms. It is evident that there are a set of functions, the activity of which is closely related to emotional excitement, and which form a more or less definite group. What we have to assume is that this group of correlated functions or the nervous arrangement which underlies them, form one of the weak points of the nervous system. When the nervous system as a whole suffers a severe strain, this is one of the places through which the line of fracture, so to speak, is liable to run, just as under other circumstances it runs so as to produce progressive muscular atrophy, or epilepsy, or hysteria; and when either of these latter disturbances occur in connection with Graves' disease, it is probably because the nervous system of the individual concerned has given way simultaneously in more than one direction. Usually, when the nervous system gives way at one or another point, it is possible to find some locally acting cause which made that point especially weak for the time being. This may be one of many relating causes, such as an inherited local weakness, an exceptional local strain, or, in the case of Graves' disease, local irritation of various sorts, or a temporary paralysis of the central vasomotor system. It is to the great merit of the French school to have enlightened us on these various disturbances which form what they call *the neuropathic family*, and with skill and clearness to have pointed out the relation between them. Raymond and Serieux have done this for exophthalmic goitre[1] in an interesting and valuable paper. If the lines that they draw between the different nervous

[1] *Rev. de. med.*, 1892, No. 12.

affections to which they refer are too sharp, we may pardon the error for the sake of the practical value of the picture which they present. The opinion of these writers is essentially that which I have thus attempted briefly to state. They believe, that Graves' disease may be best conceived of as a disorder of the nerve arrangements in the pons and medulla, which enter into activity as a part of the emotional expression. When to this group of phenomena other nervous symptoms are added (mental symptoms, &c.), or signs of an exaggeration or giving way of other nerve activities, they consider that we have to deal, not with additional symptoms of Graves' disease, but with a series of more or less independent affections, co-existing, because all are similarly expressions of one morbid influence, namely the neuropathic state. These writers quote Peter[1] as pointing out a resemblance between the symptoms of Graves' disease and those of strong emotional excitement. But so far as the priority of conception is concerned, this view was advanced by an English writer a number of years ago (reference now unknown to me). In this connection I refer also to Darwin's work on emotion in animals. For that matter the idea is so striking that it has doubtless suggested itself to many minds independently. It is certainly a merit of the French conception of the tendency of these neurotic manifestations to show themselves coincidently that it helps us to understand the diversity of the clinical pictures presented by different patients suffering with Graves' disease. The idea would be that as the nervous system breaks down in one direction, this very fact is liable to render it more prone to break down in others on account of the excesses and excitations to which the first sickness gives rise.

There is one other mode of view of the pathogenesis of Graves' disease to which it is important that a few words should be given. This is the conception of it as due in part to excitation of the nerves coming from the vagus and sympathetic, which ramify so plentifully in and around the thy-

[1] *Bull. med.*, April 23, 1890.

roid gland. This view is ably presented by Wette[1] on the basis of a large experience with the surgical treatment of goitre of all sorts. A somewhat similar position is taken by Mueller.[2] Both these writers believe that the nervous symptoms which are so common as an accompaniment of ordinary goitre pass over by insensible gradation into those which are characteristic of typical Graves' disease, though Wette inclines to the view that in the latter case symptoms are superadded, which he considers to be probably due to toxic products from the affected gland. Two of the cases of ordinary goitre reported by Wette are especially important, because they indicate how ordinary goitre is liable to affect the heart independently of the symptoms of Graves' disease. These are cases, namely, where the heart's action seemed to have been *slowed* by the irritations starting from the goitre, and we can imagine that this might happen often were it not that, as he says, the inhibitory arrangements on which this slowing depends are always the first to suffer under over-stimulation.

It is, indeed, improbable that the thyroid gland, with its rich nerve supply, should swell and pulsate and become filled with masses of new connective tissue without giving rise to nerve excitations, especially in view of the fact, to which I have already alluded, that irritations in the nasal cavity seem to act as the source of so many reflex symptoms, among which are occasionally exophthalmos and perhaps other of the signs of Graves' disease.

To sum the whole matter up, we have two questions to bear in mind as regards the ætiology of Graves' disease: First, what is the underlying predisposing cause? Second, what is the mechanism by which this cause acts? The underlying cause I believe to be an undue excitement of the quasi-physiological arrangement called into play frequently as a part of emotional excitement. This arrangement represents the channel into which emotional excitement naturally pours itself after rising to a certain height, and its

[1] *Arch. für Klin. Chir.*, p. 44, 1892.
[2] *Deut. Arch. für Klin. Med.*, 1893.

anatomical centre is in the medulla oblongata, and related parts.

As regards the modes in which this nerve arrangement underlying the symptoms of Graves' disease is actually disturbed, they may be many, and among them there seems it may be that poisoning by the thyroid secretion is one active agent. This is, however, a matter of some doubt, because we have no right to assume that if the symptoms of Graves' disease are habitually due to the toxic action of the thyroid secretion, they are still capable of being excited in the same form without the aid of that secretion, and if we can get, as it appears, the greater part of these symptoms under quasi-physiological conditions, then it would seem unnecessary and somewhat gratuitous to invoke the thyroid secretion as an habitual cause of them in disease. Neverthless, it would appear that the physiological action of the thyroid extracts does excite a series of symptoms somewhat resembling those of the affection with which we are dealing.

[The exhaustive, historical and analytical monograph on Basedow's disease, by Leopold Hirsch (*Sammlung Klinischen Vorträge*, 1894) came to my notice after this paper was prepared, so that I have not attempted to utilise it fully. The author's careful analysis makes it clear that the time is not ripe for accepting any exclusive theory of the causation of the disease before us.]

As regards the *treatment* of Graves' disease, the following facts are to be borne carefully in mind: First, in the early stages of the disease it is often possible to effect an improvement or cure by the removal of the exciting cause, combined with the use of such influences as will secure the most absolute physiological rest to the nervous system. Occasionally chlorosis seems to act as such an exciting and removable cause (Robertson); at other times the irritation of some certain nerves; while in other cases the only obvious factor has been a strong emotional excitement which needs to be counteracted by profound quiet, combined with tonic treatment.

Second, one cannot review the history of the therapeutics of this affection carefully without becoming con-

vinced that a long step toward recovery is made if one can bring to an end any one of the series of partial causes which are tending to maintain the disease. It is on this principle that we can explain the beneficial effect of the treatment of the nasal cavity, the removal of the thyroid gland, and the measures specially designed to quiet the action of the heart. The fact that by partial thyroidectomy we are able to remove a certain amount of secreting tissue of the gland, does not, I think, at all prove that the thyroid disease was the principal or only cause of the affection. What we probably accomplish in that way is the removal of a part of the excitations which combine to keep all the unstable nerve centres in an irritable state.

The records of the result of operation on the thyroid seem very favourable so far as they have been reported. Out of more than fifty cases there have been three or four deaths, and in almost all the rest a greater or less degree of improvement has resulted, frequently a substantial cure. Nevertheless, the operation should count as a dangerous one, especially in cases of weak heart. In two cases observed by myself,[1] however, the results have not been so favourable as I had been led to hope. One patient died at the end of a week, though apparently doing well. The other patient is better than before the operation, though by no means well. The thyroid at first diminished in size, but is now increasing again. I have also seen a case where a relapse occurred two years after the operation.

It happens not infrequently that an operation is followed by paresis or paralysis of one recurrent laryngeal nerve. This happened in my first case, and the paralysis has not passed away, though the voice has returned. An operation has been devised to prevent this, which consists in leaving the back part of the gland with its attachment, and removing the anterior half (Miculicz).

It is very desirable in making further studies of the effects of the operation that surgeons should pay special attention to the symptoms of the first few days after the

[1] *New York Journal of Nervous and Mental Diseases*, December, 1893, and May, 1894.

operation, in order to test the correctness of the theory which I have advanced that a patient suffers from thyroid poisoning during that period.

The indications for and against surgical operation have been very recently, though briefly, discussed by Rehu.[1]

He thinks that operative treatment of the goitre in one or another way is the treatment *par excellence* for Graves' disease, but that if thyroidectomy is undertaken in advanced stages of the disease, or when the heart is excessively weak and irritable, it is attended with great danger. Two of his patients died from cardiac failure shortly after the operation, and it is noteworthy that in one of these cases the operation consisted only in ligaturing the thyroid arteries, so that there is no reason to accuse thyroid poisoning as having been the cause. Another patient died of pneumonia, and a fourth died on the operating table from the effects of tying the stump of the gland to check hæmorrhage. Rehu has seen benefit, in light cases and in early stages of the disease, from injections of iodoform, and recommends ligature of the arteries for very vascular goitres.

As a rule, however, he thinks resection is the best method, and that it should not be delayed until the patient is *in extremis*. Personally, I do not feel that the last word has been said with regard to the dangers of the operation or as to the means of anticipating or avoiding them.

As regards the drugs which have proved of benefit, the two most important are probably iron and belladonna. It has been suggested that belladonna acts by diminishing the secretions from the diseased thyroid gland, but it is also well known to quiet the heart in certain conditions independently of the other mode of action. I have not seen much benefit from its use. Picrotoxin was recommended by Bartholow, but Robertson tried it without any effect. Ergot occasionally seems to be useful, and iodide of mercury ointment, or some other form of iodine ointment, seems to act beneficially in reducing the size of the enlarged thyroid gland. Mental and physical rest are, however, besides thyroidec-

[1] *Loc. cit.*

tomy and the treatment of the chlorotic and anæmic conditions, undoubtedly the most effective.

A patient of mine who had been severely ill for many years began to improve the moment when she commenced to lie in the open air many hours daily, and this practice she continued with benefit both winter and summer.[1] Eventually the thyroid, which had never been more than moderately large, practically disappeared, the heart's action became almost normal, and the exophthalmos much less, so that the patient has returned to moderately active life.

[1] See also, J. Madison Taylor, *Medical News*, December, 1893.