Observations

ON

EXOPHTHALMIC GOITRE*

BY

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Exophthalmic goitre is a mysterious disease, and of its pathology we are very ignorant. We know many isolated facts about its causes and onset, but it is difficult to correlate these and to give each fact its proper position in the aetiology of the disease. Thus there is little doubt of the correctness of the following facts, though they advance us very little in assigning a true pathological cause:

The disease is far more common in women than in men, in blondes than in brunettes, and in single women than in married ones.

It almost always causes more enlargement of the right side of the thyroid than of the left.

It exhibits a slight tendency to frequency in certain parts of the world, but these localities are not usually those where ordinary parenchymatous goitres abound.

It is rarely seen at the extremes of life, being uncommon under the age of 15 and over the age of 55.

It seems to be rather commoner in some professions and walks of life than in others. School teachers exhibit a marked tendency to develop it, and it is certainly seen more in brain workers than in manual workers, while it also tends to produce a type of woman who is volatile, lively, and temperamental, and who, if the disease is not too far advanced, is usually of a type distinctly attractive to the male.

These are all mere unexplained facts, but there are other features of which we are tolerably certain. Thus, most of the symptoms and physical signs are due to a substance produced in the thyroid gland, which is nearly always enlarged. This substance is either an altered and toxic secretion, or possibly an excessive amount of normal secretion. The thyroid gland, therefore, may be looked upon definitely as the factory where the symptoms are produced. That there is, however, some underlying primary cause responsible for the changes in the thyroid gland itself cannot be denied, and there is a considerable body of evidence pointing to an infective causative agent of some sort—possibly intestinal. In support of this is the fact that in many cases the patient dates the onset of the disease from some kind of febrile attack, often referred to as "influenza," while it is not uncommon to find the spleen definitely enlarged. There is, however, so far no proof of the existence of this infective agent. There is also very little doubt that the other ductless glands are involved in the process, and play a certain part in the production of the symptoms; the suprarenals especially are important in this connexion, and it is quite possible that some of the physical signs, such as the exophthalmos, are directly due to suprarenal influence. The thymus also is nearly always found to be enlarged. Again, it is not uncommon to find a direct connexion between this disease and diabetes, and the two conditions may exist together. However this may be, in the present state of our knowledge we believe that these other ductless glands are affected secondarily to, or possibly as a compensation for, the state of the thyroid, and that it is the alteration in the thyroid gland itself that is the basis of the disease.

DEFINITION

It is very important in any discussion of this disease to remember that a correct definition of the term "exophthalmic goitre" is difficult, that between the

ordinary parenchymatous goitre with no toxic symptoms, the simple thyroid adenoma with nervousness, tremor, and rapid pulse, and the well-marked case of Graves's disease with its classical syndrome, there are an infinite number of different grades of severity, and that occasional clinical curiosities are found, such as: marked toxic hyperthyroid symptoms with no appreciable enlargement of the thyroid gland; unilateral exophthalmos instead of the common bilateral type; or—by no means uncommonly—malignant disease of the thyroid, associated with exophthalmos, palpitation, rapid pulse, tremor, and nervousness. I do not, therefore, regard any case as deserving of the name of Graves's disease unless it presents a certain amount of eye change, a rapid pulse, and definite cardiac changes—slight enlargement in the milder types, and considerable dilatation, with fibrillation and alterations in the heart sounds, in the more advanced cases. Moreover, in all cases in which these toxic symptoms are mild enough to raise any doubt as to whether the condition should really be called Graves's disease or not, before the diagnosis is actually settled a microscopical examination of the gland should be made to see if the hyperplasia and changes in the epithelium, which the exophthalmic thyroid gland always shows, are present.

Primary and Secondary Graves's Disease

The distinction between primary and secondary Graves's disease is undoubtedly a useful one, both in diagnosis and in treatment. By primary Graves's disease we mean that type where the toxic symptoms have been present from the first, and more or less coincide with the appearance of the goitre, while secondary Graves's disease is the name applied to those not at all uncommon cases where a goitre (either adenomatous or parenchymatous) has been present for some time—often many years—before the full range of toxic symptoms comes on. Primary Graves's disease is usually much the more severe form, and it is usually in this class that the desperately bad cases are found. Secondary Graves's disease shows a particularly marked tendency to give rise to auricular fibrillation, but the results of operative treatment in secondary Graves's disease are even better than those in primary cases, even though marked auricular fibrillation be present. It is possible, or even probable, that in primary Graves's disease we are dealing with an altered and toxic thyroid secretion, and in secondary Graves's disease with an excess of a normal thyroid secretion.

When discussing exophthalmic goitre, therefore, it is best to refer only to the true Graves's disease, and not to such conditions as cysts or adenomata of the thyroid, with nervousness and a rapid pulse, or to parenchymatous goitres in nervous women. The true Graves's disease is naturally a very much more serious condition.

The cases one encounters clinically vary considerably, according to whether the main stress of the disease falls upon the nervous system, the cardiac system, or the abdominal organs. Marked affection of the nervous system, with tremors, jumpiness, excitability, and even mental changes, seems often to be associated with marked exophthalmos and a large, very hard, rounded, prominent goitre, though it must be remembered that the goitre of Graves's disease never reaches the very large size which a parenchymatous goitre may attain. On the other hand, in the more truly cardiac type of case, where severe dilatation and fibrillation occur, the goitre is usually softer and less definitely prominent, while exophthalmos is less marked, but pigmentary skin changes are often present. The abdominal type of case with much diarrhoea and vomiting often appears to be intermediate between the above two types.

As regards eye changes, though the exophthalmos is often very marked, there is a very early change sometimes seen in the eye before any prominence of the eyeball or von Graefe's sign is present, which is, I think, almost certain evidence that eye changes are commencing; and this is a peculiar shininess or glinting of the cornea, which is often noticeable at some little distance from the patient.

* Extracts from a paper read to the Guildford Division of the British Medical Association.

CHOICE OF TREATMENT

Several methods of treatment exist, each of which has its own advantages, disadvantages, and risks. Briefly, we are faced by the possibilities of treatment by various medical methods, by x rays and radium, and by surgery.

While there is no doubt that exophthalmic goitre is a disease which is serious, grave, and unpleasant, it is by no means always necessarily fatal. It is difficult to estimate mortalities, but probably about 25 to 50 per cent. of cases of Graves's disease will ultimately die of it if left untreated, while of the remainder a few will undergo a spontaneous cure, though this will take many years and there may be relapses. The majority will develop into chronic invalids, liable to be carried off by any slight infection, able to hang on to their lives but unable to do anything with them, and these points must be taken into account in estimating both the value and the necessity of any particular form of treatment.

Medicine

Treatment by medical means can certainly offer a fair chance of a cure in early cases, and, in others, a very reasonable chance that, with a careful and sheltered life, the patient may live to a good old age. At the same time it will have to be very prolonged, and it is not likely that even mild cases will get well under several years, while the more severe the case is the less likely is any permanent benefit to accrue. Temporary benefit is nearly always produced by medical treatment in every type of case, but unfortunately relapses are only too frequent. In connexion with this it is remarkable that Lugol's solution of iodine, given in 10-minim doses, nearly always produces a marked improvement, which, however, only lasts for two or three weeks as a rule. Most surgeons, therefore, make a practice of giving Lugol's solution for ten days or so before any operative treatment is undertaken, but it should not be continued for longer than this.

X Rays and Radium

The results of x -ray treatment are not very impressive. It is uncertain and not free from the risk of producing myxoedema. It is undoubtedly capable of producing improvement in some cases, but cures are very rare indeed and relapses very common. Moreover, the surgeon cannot help having a personal objection to it, because he often has to operate upon cases which have previously received x -ray treatment, and the operation is rendered definitely more difficult because of the increased adherence and vascularity of the gland. There may be no more difficult operation in surgery than the removal of a thyroid which has previously had x rays on it. Radium, on the other hand, does seem to be more useful in specially selected cases. Where other methods of treatment have failed, or when operation is impossible, radium applied externally over the goitre has sometimes produced marked improvement. This has been especially so in cases which are showing mental changes.

Surgery

Surgical treatment has always seemed a reasonable procedure, and there is no doubt now that operations can be performed, even in severe cases, with a mortality that is very slight, and that they result in vast improvement in the patient's health. A recent series of 650 cases of Graves's disease, published in *St. Thomas's Hospital Reports*, has shown that the mortality of all cases treated in the surgical wards is about half that of all cases treated in the medical wards.

Many surgical procedures have been devised. Excision of the cervical sympathetic is quite useless, and ligation of one or more of the thyroid arteries is very seldom done now. There is a consensus of opinion among surgeons, which is shared by many physicians, that removal of very large portions of the thyroid gland is the procedure of choice; for though we do not know the primary cause of the disease—that cause which leads to the enlargement of the thyroid—there is abundant evidence that the enlarged thyroid is what we may call "the factory of the symptoms," and that by reducing its activity we can relieve these symptoms and render the patient a normal individual again.

CHOICE OF OPERATION CASES

One of the most important points to be considered is the selection of those cases in which operation is likely to be most suitable and successful. There are very few cases in which it is not advisable to prescribe a course of medical treatment first before considering operation. The mild cases may be cured by this, while the severe ones will become fitter and better, and more able to stand the operation. Among the last 900 cases I have seen there have only been three which have been refused the chance of operation on the ground that they were too advanced for surgery to hold out any hope of benefit. But there are many cases to be seen in which the symptoms are so slight that one may well wonder whether operation is really worth while, or whether other methods of treatment should not be tried first. In connexion with the surgery of Graves's disease another reference must be made to medical treatment. In very severe cases medical treatment, in the form of absolute rest in bed, diet, strontium bromide, Lugol's solution, etc., is most valuable as a preliminary to, and a preparation for, the operation, frequently rendering the patient fitter to stand the strain of the latter. On the other hand, in moderately severe cases, or where one sign or symptom is present to any marked degree or is progressing, medical treatment, though useful as a preparation, should not take the place of operation, for it does not lead to so marked, so permanent, or so rapid an improvement, and in such cases it should not, in my opinion, be continued for more than two or three months. If the operation is undertaken reasonably early, not only is the patient in a better condition to stand it, but a better result is likely to be obtained in the end and much time and trouble saved.

I would lay particular stress upon this question of time and trouble for the patient, for many cases of Graves's disease, by careful medical supervision and treatment by means of repeated long rests in bed, are enabled to carry on semi-invalid lives for long periods, whilst were they to undergo surgical treatment early in the complaint, their return to health would come very much sooner and be much more complete. The operation mortality has now proved to be so small that the risk may very justifiably be run in an attempt to obtain a cure for a disease of so serious a character. In this way the position of the surgical treatment of Graves's disease is not unlike the position of surgery in the treatment of gastric ulcer, for the economic and the time-saving factors must be considered in both. In mild cases there are not any actual contraindications to operation, other than independent gross constitutional disease, but there is always the question as to whether the disease is sufficiently severe to warrant exposure of the patient to the discomforts and expenses associated with an operation. In the more severe types we have before us a large number of signs and symptoms for consideration, and I do not consider that irregularity or great rapidity of the pulse, even up to 200, marked cardiac dilatation, or fibrillation necessarily contraindicate operation. Fibrillation, in particular, is often enormously improved soon after a thyroidectomy—often within two days—and fibrillating cases do so well that I would almost go so far as to say that I prefer them! Nor do diarrhoea and vomiting, marked loss of weight, or the presence of acetone in the urine, prevent operation, provided that it is done under a suitable anaesthetic, that the mental condition of the patient is moderately good, and provided still more that she is willing and anxious to have the operation done.

Nervousness and emotional instability are, of course, nearly always present, and even though these are very marked they do not constitute any bar to operation; but if mental symptoms of a maniacal, delusional, or melancholic type are setting in operation does not appear to hold out a reasonable prospect of improvement, and may, in fact, make the patient's condition worse than before.

One is occasionally asked to see, with a view to operation, patients who are, to all intents and purposes, certifiable lunatics, and who have enlarged thyroids (often with other signs pointing to Graves's disease), but, needless to say, thyroidectomy is not likely to benefit them.

Five patients of this kind, with more or less marked signs of Graves's disease, and delusions, suspicions, or melancholia, have been treated by the application of radium. Two of them are no better, one is much improved, and the other two appear at present to be quite well. It is, however, too early to feel certain that the radium is responsible for this, but it appears to be quite worth while to use it again in similar cases.

There are other associated conditions which entirely negative operation—namely, an age of over 65, the presence of diabetes or other gross constitutional disease, great fear or unwillingness to undergo operation, and the presence of oedema due to a failing heart. As is well known, the majority of sufferers from this complaint are women, and they appear to derive more benefit from the operation than do the male sufferers.

CHOICE OF ANAESTHETIC

The question as to which form of anaesthetic is preferable for these operations has recently given rise to much discussion. There is little doubt that chloroform is highly dangerous to patients suffering from thyroid toxæmia, and if a general anaesthetic is to be given at all it must consist of ether, and as little ether as possible. Given by means of the intratracheal tube, ether is convenient for both surgeon and anaesthetist in all operations about the head and neck, but in exophthalmic goitres these advantages are apparently outweighed by the facts that (1) a considerable depth of anaesthesia is required at first in order to pass the catheter into the trachea, and (2) the passage of this catheter entails a certain amount of manipulation of the neck, while the fewer manipulations there are throughout this operation the better. For these reasons ether, if used at all, is better given on an open mask. Though the milder cases can be operated upon safely under open ether, rectal ether, or gas and ether, the severe cases are subjected to a much smaller risk under local anaesthesia. Recently, in all except the very severest cases, we have been using avertin in the rectum, combined with a minimal amount of gas and oxygen, or, in the very bad cases, combined with local anaesthesia. In several hundreds of cases we have so far had no trouble at all. The dose of avertin should be slightly greater per body weight than one would give to ordinary abdominal cases. We therefore make a practice of doing a thyroidectomy on these patients under some special form of light open anaesthesia, except in the very severe cases. Here a local anaesthetic is far safer, and in some severe instances one can do the operation comparatively safely by this means when one simply would not dare to give the patient a general anaesthetic at all. This applies especially to the cases where the heart is grossly disorganized, the apex beat perhaps in the axilla, and, often, marked fibrillation present. If a local anaesthetic is being used the patient is rendered sleepy or semiconscious either by means of avertin or by a large dose of paraldehyde in the rectum, or of morphine hypodermically some few hours before. Hyoscine is best avoided. The operation of thyroidectomy, performed under local anaesthesia for an adherent and highly vascular exophthalmic goitre, is naturally somewhat of a strain for both patient and surgeon, but with a combination of coaxing and cunning it can usually be done perfectly satisfactorily. If asked whether they would prefer a local or a general anaesthetic women patients, at any rate, will often choose the local; men do not tolerate it so well.

AMOUNT OF GLAND TO BE EXCISED

Another exceedingly important consideration in connexion with these operations is the amount of gland tissue that should be removed. It cannot be too strongly emphasized that removal of one thyroid lobe (hemithyroidectomy) is hardly ever sufficient completely to cure a case of Graves's disease, and that, if a permanent cure is aimed at, it will be necessary to remove one lobe, the isthmus, and a third, or even two-thirds or more, of the opposite lobe, according to circumstances. It is usually feasible to do all this at one operation, but occasionally, where the gland is abnormally adherent (as after previous

x-ray treatment), or where the patient is exceedingly ill—it has to be done in two separate stages, one lobe being removed at the first operation, while later on a portion of the other lobe is excised.

There is very little chance of removing too much gland, provided the patient can stand it, and I have several times removed the whole gland. But all surgeons are painfully conscious of having, on occasions, not removed enough of the gland. Removal of one lobe will always produce considerable improvement, but it is not the best that can be done, and hardly ever cures the symptoms. There have been many cases in the past in which one lobe, or even more, of the thyroid gland of an exophthalmic patient with a large goitre has been removed, and yet the patient still has left in the neck, after the operation, thyroid tissue far greater in amount than that of the normal gland. How can this possibly produce a cure? It is all-important to remove sufficient gland tissue, and provided that a piece the size perhaps of one normal thyroid lobe or even less is left in the neck one would theoretically like to remove all the rest. The practical limit to the amount that can be removed is, of course, set by how long or how severe an operation the patient's condition is equal to; for a long thyroid operation, especially if done under local anaesthesia, is undoubtedly exhausting for both patient and surgeon. Thus it is not always possible to remove quite as much thyroid tissue at a time as one would like; the necessity for a second operation may then arise.

The danger of leaving too little thyroid behind in the neck is not real, for exophthalmic thyroids are curiously apt to have outlying nodules and large lobes projecting behind the larynx on both sides, and there is probably always more thyroid tissue left *in situ* than would appear, even after extensive removal. Moreover, quite a small quantity of the gland tissue found in this disease seems to be sufficient to keep off any symptoms of myxoedema and to preserve the normal thyroid balance of the body. One cannot leave the question of extensive removal of the thyroid tissue without some reference to the parathyroid bodies and their supposed association with tetany. For many years I knew of no surgeon who had had a case of real tetany after thyroidectomy, but recently I have seen two. Nevertheless, it seems that in the performance of the operation the parathyroids may really be almost completely ignored.

DETAILS OF OPERATIVE TECHNIQUE

It is the practice of some surgeons, when performing thyroidectomy, to leave *in situ* shavings of the posterior surface of the gland in the neighbourhood of the inferior thyroid artery, with a view to protecting the recurrent laryngeal nerve; but this should not be done—at any rate when dealing with cases of Graves's disease—for these small portions of gland tissue are capable of undergoing, and do undergo, growth and hypertrophy, and later may increase to such a size that their internal secretion is sufficient to cause a recrudescence of the symptoms and a failure of the operation. It is therefore of the greatest importance that the gland should be cleanly dissected out and no outlying shavings left behind. This applies equally to that stage of the operation when the superior thyroid artery is being tied and cut; this must be done cleanly above the gland, and portions of thyroid tissue should not be left on the stump of the artery, though it is tempting to leave them when the superior thyroid pole lies high up in the neck and is difficult to reach. The retrolaryngeal lobe should also be removed, at least on one side.

The recurrent laryngeal nerve, which divides up into branches some little distance away from the larynx, is at times very closely incorporated with the gland substance, and damage to this nerve may be a most serious accident for the patient. Apart from being cut or tied in a ligature—which should never occur—the nerve is remarkably sensitive to handling, pinching, bruising, or stretching, and minor insults which would have no effect on most of the nerves in the body may be sufficient to put this nerve or its abductor fibres out of action for many weeks. It should not be in danger if the wound is kept dry and

the dissection is carried out with a blunt instrument kept close to the gland substance. The gland is usually tightly adherent to the trachea at one point in front, and though a blunt instrument has been used to separate it at the sides, the scissors will nearly always be necessary to effect the separation from the front and central portion of the trachea. There is no need to lay stress on the special difficulties of this operation—the true exophthalmic gland has outlying lobes and nodules, and is very hard, exceedingly vascular, friable, and adherent. This may render very difficult the process of dislocating the lobe and lifting it up to separate it from the trachea, while the patients, if the disease is at all advanced, stand loss of blood very badly, and every effort must be made to diminish haemorrhage. The veins are usually more troublesome than the arteries—as in all branches of surgery—and though a local anaesthetic has the effect of making the superficial tissues avascular, it has no such effect on the deeper ones. Further, the fact that the patient is not unconscious makes a haemorrhage, should it occur, more difficult to deal with.

The mortality of this operation in the last 900 cases has been $2\frac{1}{2}$ per cent.

RESULTS OF TREATMENT

It may well be asked, "What are we to expect from this operation in the way of improvement?" and the first question that the patient will ask is probably about the mortality. A mortality of $2\frac{1}{2}$ per cent. is not unduly high when one is dealing with so serious a complaint. This disease leads inevitably to prolonged and often very serious ill-health, and gives rise to symptoms which are most unpleasant to the patient and even to her friends—especially the incessant palpitation and rapid action of the heart, the nervousness, jumpiness, and the sleeplessness. Moreover, in many cases—especially in women over 40—it leads to gross disorganization of the heart and to death. It is without doubt justifiable to run a small amount of risk in an attempt to effect a cure. Nevertheless, one cannot help regarding all patients with a certain amount of anxiety for the first two or three days after operation.

Of the twenty-two patients in this series who succumbed eight died of pneumonia within the first four days, and the other fourteen within sixty hours of the operation with the symptoms of what one is accustomed to call acute hyperthyroidism. After three or four days, therefore, any danger of death would seem to be over. Following the operation there usually appears to be an improvement, which is more marked and rapid in the subjective symptoms than in the physical signs, and patients often look and feel much better within a few days of the thyroidectomy. It is often not for a month or so that really marked improvement in the physical signs sets in. This improvement in subjective symptoms often disappears after a few weeks, when the patient goes back to her own home, but reappears later as a permanency in two or three months, and is then accompanied by marked improvement in the physical signs. A long rest for some months after the operation is absolutely essential.

As a rule, after three or four months we find that patients who have had an adequate amount of thyroid gland tissue removed feel well, eat well, sleep well, and can do their day's work, though I do not think it wise for them to recommence their normal life quite as soon as this. Though they look and feel well and put on weight, it is frequently found on examination that the pulse rate, while very much slower than it used to be, has not quite come down to the normal, remaining between 80 and 90, and that the cardiac dilatation, though considerably less, has not quite gone. Irregularity of the pulse, acetonaemia, and diarrhoea, if previously present, almost invariably disappear, and the nervous excitability, tremor, and jumpiness are greatly improved; but the exophthalmos, though much less marked than before operation, rarely if ever vanishes completely. Those patients who receive surgical treatment for the condition comparatively early in its course—that is, before they have developed the gross degenerative conditions of the myocardium and of

other viscera that set in sooner or later—should all, if a sufficient amount of thyroid tissue is removed, become well in the sense that they should be able to lead a normal life, do their ordinary work, and sleep the sleep of the just. On the other hand, it is no use pretending that operation on a case with a grossly dilated and fibrillating heart and advanced myocardial degeneration will ever make that heart perfect again, although it will make it very much better. Palpitation and shortness of breath—two symptoms especially unpleasant to the patient—usually show the greatest amount of improvement.

As regards the effect of the operation on the loss of weight, which is often so serious a feature in a bad case, the gain in weight following operation is nearly always marked, and may even become embarrassing. Another very satisfactory feature about this branch of surgery is that, as a general rule, the bad cases appear to derive more improvement from, and to be even more pleased with the results of, the operation than do the slighter cases.

As in other diseases, it is difficult to compare and contrast the results of treatment by merely observing symptoms and physical signs, and it is therefore satisfactory to find that there appears to be a method by which one can attempt to measure what we may call the "physiological fitness" of these patients before and after operation. Many of these patients have had their basal metabolic rates estimated before and after operation; before operation they are nearly always 40 to 80 per cent. above that of the normal individual—this presumably representing increased tissue metabolism as a result of the hyperactivity of the thyroid. After the operation these rates fall, within a few weeks, to amounts varying from normal to + 25 per cent. above normal, and this appears to be a fixed method of estimating the "physiological improvement." There have so far been only two or three cases in which, after operation, this basal metabolic rate has fallen slightly below normal, to amounts varying between - 5 and - 10 per cent., and these patients have not, up to the present, shown any signs clinically of hypothyroidism.

Of the success of surgery in suitable cases of Graves's disease there is, I think, no doubt, but one cannot help feeling conscious that in removing thyroid tissue one is really treating symptoms and not causes, and that the primary cause is something further back and not yet removable.

THREE RECENT CASES OF ENCEPHALITIS LETHARGICA

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During the last three years a comparatively small number of cases of encephalitis lethargica have been notified. Considerable doubt has existed in the minds of many as to how far these notified cases are really encephalitis, seeing that the difficulty of diagnosis is unusual in this disease. In the last few months there have been admitted under my care at the General Hospital, Birmingham, three cases of a somewhat fulminating character in which a post-mortem examination has permitted confirmation of the diagnosis. The type of disease in these cases resembles to some extent that which was seen in the very early stages of the epidemic in 1918. Very few of such cases have been seen in the Midlands during the last few years. It is of interest to note the existence of this severe type of case during this year, as it is possible this means that a further visitation of encephalitis in epidemic form