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THE TREATMENT OF TOXIC GOITRE.

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BEFORE we can discuss the treatment of toxic goitre, it is necessary for us to have a clear conception of what we are attempting to treat.

By a toxic goitre we mean a goitre which produces symptoms other than those due to its presence or size in the neck, the chief of which are tremor, muscular weakness, tachycardia and other disorders of cardiac function.

Now, although in practice we meet with almost every gradation in type among the toxic goitres, yet when we are considering treatment and prognosis we can divide them roughly into two. These two types I like to refer to as primary Graves' disease and secondary Graves' disease.

Primary Graves' disease or exophthalmic

goitre is, as you know, a symptom-complex marked by certain definite changes in the thyroid gland associated with changes in many of the other internally secreting glands. The changes in the thyroid gland itself vary with the severity of the disease, but in a fully-developed case they are characterized by the entire absence of colloid storage, and by the presence in the lymphatic spaces of thin watery secretion which can be demonstrated by special staining methods, as Scott-Williamson has shown. The cells of the gland are markedly granular and hyperplastic, and are often several layers deep, and there may even be papilloma formation. This condition of the thyroid is associated with the fully-developed picture of exophthalmic goitre as you know it, with tremor, tachycardia, muscular weakness, exophthalmos, and the usual vasomotor disturbances in the skin. The other internally secreting glands are involved, as is shown by the almost constant hyperadrenalinæmia, by changes in sugar tolerance, &c. Primary Graves' disease is a polyglandular syndrome in which the thyroid

by virtue of its physiological dominance plays a leading rôle, but it is not primarily a disease of the thyroid gland, and I feel certain, in spite of what I shall have to say to you presently, that in the future its treatment will be along biochemical lines.

Secondary Graves' disease or, as it is sometimes very badly termed, Plummer's toxic adenoma, is on the other hand essentially a disease originating in the thyroid gland. The usual story here is of the presence of a non-toxic goitre, usually, but not always, a nodular one, without any general symptoms for a number of years, usually more than ten. Then and generally for no apparent reason toxic symptoms begin to arise. The symptoms are those we associate with primary Graves' disease, except that the exophthalmos and other eye signs are usually absent, and the heart changes are rather different. The condition here is essentially a local one. The presence of the goitre irritates the surrounding gland, its cells are stimulated into over-activity and a condition of thyrotoxicosis due to the production of an excess of normal secretion results. In sections of such a gland smaller or larger areas in the gland, or even in the goitre itself, are found which exactly resemble the picture of primary Graves' disease, but elsewhere the ordinary picture of normal colloid storage is present. In this condition of secondary Graves' disease we are dealing with a true hyperthyroidism of local origin, whereas, as we shall see in primary Graves' disease, there is reason to believe that the state of affairs represents a disordered as well as an excessive secretion. In primary Graves' disease or exophthalmic goitre the thyroid cells are driven into a condition of over-activity by causes arising outside the glands, but into the nature of these it would not be profitable to enter to-day, as this is a field of many theories with few facts on which to base them. Nevertheless, if we accept the broad principle that primary Graves' disease does in fact arise from causes outside the thyroid gland, it follows

from this, firstly, that the ideal treatment when it is found will be one dealing with these causes and not with the thyroid, and secondly, that however much we may benefit the patient by surgical treatment of the thyroid gland, we cannot hope in the strict sense of the word to cure the condition by such means.

At present there is no specific medical treatment for primary Graves' disease, as evidenced by the fact that some 200 drugs have been credited with its cure. Medical treatment at present must consist in such general measures as rest, fresh air, a low protein diet, together with bromides, arsenic, and so on. I have purposely omitted to mention iodine as a method of medical treatment because, as I hope to show you, I consider it is very unfair to the patient to give iodine except after consultation with the surgeon. The one sure fact about primary Graves' disease is its invariable association with hyperplasia and over-activity of the thyroid secreting cells. At present our sole method of cutting short the disease is by reducing the amount of secreting tissue either by radiation or by surgery.

Personally, my experience of radium or X-ray therapy in exophthalmic goitre has on the whole been unsatisfactory. An occasional case does well, but in the majority the difficulty of judging dosage, and the varying response given by the thyroid, together with the impossibility of judging the actual size of the thyroid from outside, and therefore the amount of tissue one wishes to delete, makes radiation therapy too uncertain a weapon to be used with any confidence. The chances of producing myxœdema are undoubtedly greater than with surgical treatment, and once rays have been employed operation becomes definitely more difficult and therefore less safe. I therefore find that I only use radiation therapy if the patient or her relations definitely and finally refuse operative treatment.

When a case of primary Graves' disease

is treated medically, that is to say, when the thyroid is not directly interfered with, the duration of the disease is a long one, and during the time of its duration the patient is necessarily a semi-invalid. Not only is that the case, but the irritability and emotionalism of these patients makes them exceedingly difficult to live with, and a good deal of domestic unhappiness is generally added as well. The mortality under medical treatment is difficult to assess accurately, and the objection is usually made to published figures that they include cases too bad for surgery. On the other hand, as they usually include also a number of cases too mild for surgery, I think the two extremes balance one another. In different series of cases given by different physicians the mortality is usually stated to be between 10 and 15 per cent., the cause of death being most commonly some intercurrent infection such as acute tonsillitis.

There can, I think, be little doubt that in the present state of our knowledge of exophthalmic goitre the best method, and in fact the only method, of accurately controlling the disease is by surgical treatment. As I have already said, by the very nature of the condition surgery cannot offer a true cure, but we can hope to achieve by surgery a fourfold object. In a proportion of cases we can save life by cutting short a rapidly increasing intoxication; secondly, we can very materially lessen the severity of all the symptoms of the disease, and we can abolish some altogether; and thirdly, by so doing and by enabling the patient to gain in strength and weight and emotional control, we can greatly lessen the period of invalidism. Lastly, we can prevent or cut short myocardial changes which would inevitably occur if the disease were left to itself.

With such advantages to offer, and with so little alternative before the patient, it is obvious that surgery must be the treatment of choice, provided always that surgical treatment can be made safe enough for the risk not to be a real objection. Naturally the

degree of risk must vary with the state of the patient, but I hope to be able to show you that even the bad risk patient can be made a reasonably safe surgical risk by appropriate treatment.

I want to discuss with you now the factors that have been concerned in bringing the operative treatment of exophthalmic goitre into the safe position which it occupies to-day. Let us first consider for a few moments some points about the natural history of the disease. Some very acute cases become rapidly worse and die in a few months, and, on the other hand, some mild cases become stationary in the first few months and never develop the full symptom-complex at all. The majority, however, run a fairly definite course extending over many years, and leaving the patient when at last it dies down with permanent changes of varying severity in many organs. During the period of its course, however, the severity of the intoxication of exophthalmic goitre is by no means uniform; it consists of a series of exacerbations which are known as crises. As a general rule, from the onset the symptoms increase in severity and, as we shall see, in number for a period of from eight to ten months, the summit of the curve being of about a month's duration and being marked by an increase in severity of all the symptoms present, and usually by the onset of some such as diarrhoea, vomiting and amenorrhoea, not previously present. After a few weeks improvement begins; although the patient does not reach anything like the normal, she becomes markedly better. Such an improvement invariably follows the crisis if the patient survives it, and as the increase of symptoms which preceded the crisis has often led to the trial of new remedies, it must be discounted in assessing their effect. Further crises, with subsequent improvement, occur during the course of the disease. They are seldom as severe as the first, but after each one the organism remains in a somewhat more damaged

condition than before. The more one sees of this disease the clearer it becomes that operation should be avoided by every possible means during the crises. I would go further and say that as a general rule it is wiser not to operate if possible just before a crisis, but to choose the period of down-grade of severity when the crisis is over. If there is any truth in what I have just said, it follows that it becomes of great importance for us to have a very clear idea of the period of the disease with which we are dealing when we first see the patient. It is comparatively easy to make up one's mind that the crisis has occurred and is over, as a history of diarrhoea and vomiting and a general increase of symptoms which have now abated, together with, and this is perhaps most helpful of all, the return of menstruation after a period of amenorrhoea, will make that plain. What is far more difficult is the situation when the patient is seen before the crisis, and where one wishes to make up one's mind whether the severity of the disease as you see it represents almost the peak of increase, and that therefore it is safe to wait for the expected amelioration, or whether you are seeing a rapidly increasing intoxication which, if not cut short, may lead to death either before or in the crisis. Now history becomes of great importance in making such a distinction, and in this connection there is a common fallacy, and that is the belief that goitre and exophthalmos are early signs of the disease. On the contrary, they are not early signs at all, but they are usually the signs from whose first appearance the patient dates the onset, and consequently merely asking the patient when her disease began is usually quite valueless for our present purpose.

Although cases do not follow any invariable rule, my experience is that the symptoms of exophthalmic goitre occur in a fairly regular sequence, the order of onset being roughly as follows: (1) Cerebral stimulation; (2) vasomotor disturbances in the skin; (3) tremor; (4) mental irritability;

(5) tachycardia; (6) exophthalmos; (7) goitre; (8) loss of muscular strength; (9) cardiac insufficiency; (10) diarrhoea; (11) vomiting; (12) mental depression; (13) jaundice; (14) death. It becomes, therefore, clear that inquiry should elicit a history of disturbance of health antedating the appearance of goitre or eye signs by some weeks or months, and that is usually so in practice, so that one can in this way correct one's orientation and avoid interfering at the time of the crisis. During the first few months surgery is seldom indicated, as one has no means of knowing whether or not the attack will abort, but every surgeon should have in his mind a standard of toxicity beyond which he will not allow his patient to go.

It is therefore most important that the surgeon and physician treating this disease should work in harmony and co-operation, and the time when the surgeon was only called in when the crisis had given rise to alarm, and the patient and her friends called for something to be done, is past. I cannot make it too clear that that is the period of the disease when disaster is likely to follow surgery, and although, as we shall see, the use of Lugol's iodine has somewhat lessened the danger, yet it is still quite a real one. Personally, and realizing that circumstances vary in every case, I should prefer not to operate within six weeks after the maximum severity of symptoms.

To summarize therefore the factors of safety in regard to time of operating, I would say: (1) Not to operate usually within the first six months; (2) not to operate within six weeks of a crisis; (3) to choose if possible the down-grade of severity rather than the up-grade; and (4) always to get a clear idea of what stage in the disease any individual patient has reached.

The next factor of safety depends on the condition of the heart, or rather of the heart muscle, and in assessing it accurately lies the great value of cordial co-operation between the physician familiar with the disease and the surgeon. The first and most

common sign is tachycardia, characterized by long and continued rapid action of the heart, the rate of which is the same in sleep as when awake. In addition to the rate, the intensity of the beat is increased, and it can be felt and sometimes even heard bounding in the chest. In women with their hats on you can see the pulsation in the trimming of their hats, and can count the pulse merely by watching them. Palpitation is the symptom complained of by the patient, and a very distressing one it is, an interesting point being that it bears little direct relation to the rapidity of the heart's action. After a period of merely accelerated rate the true thyrotoxic heart condition develops. There is a thrill and a diffuse bounding apex beat. There is considerable increase in the heart volume by X-rays, mainly due to left-sided dilatation, and this dilatation varies rapidly with the condition of the patients. There is usually a functional systolic murmur and there is capillary pulsation. After months of such over-action and relative valve incompetency, the conductivity becomes impaired and auricular fibrillation occurs. This is usually paroxysmal at first, and while the intervals between attacks and the duration of the attack vary in different patients, they are usually fairly constant for a period in the individual. Gradually attacks occur more frequently, and ultimately fibrillation becomes constant. There are certain peculiar features about the fibrillation of Graves' disease. In the first place, from the point of view of prognosis it is one of the least serious forms of fibrillation, and indeed I look on paroxysmal fibrillation as a definite call for urgent operation without any marked increase of risk. Another point is that digitalis is not as a rule a satisfactory drug to employ. In the paroxysmal stage it not infrequently induces the onset of permanent fibrillation, and in the permanent stage, while it should be tried, it is not usually of much value.

Quinidine, under the control of electrocardiographic observations, is valuable, but frequently fails to restore normal rhythm

before operation, but after operation if normal rhythm does not return by itself, which it not infrequently does, a few doses of quinidine will usually produce it.

The important thing to assess before operation is the degree of myocardial damage, and in this matter an electrocardiogram is of great assistance. It must not be forgotten, however, that the administration of iodine by itself is able to cause inversion of the T-waves, a fallacy which of course would not be overlooked by a competent cardiologist. If an electrocardiograph is not available, most reliance is to be placed on the degree of dilatation present, and present when the patient is up and about.

Dilatation of an inch or over should be looked on as calling for medical treatment for a period until it has lessened, whereas if there is less than $\frac{1}{2}$ in. dilatation the patient should, other things being satisfactory, be a good surgical risk.

There is still considerable doubt as to the exact cause of these heart changes. Actual excess of secretion does not seem to be responsible, as an intravenous injection of thyroxin will not cause tachycardia unless a solution of amino-acids is injected at the same time. What seems probable is that not only is an excess of secretion produced, but it is no longer a normal secretion, and that there is a dysthyroidism as well as a hyperthyroidism. Kendall isolated from the thyroid gland a crystalline substance to which he gave the name thyroxin, and whose chemical formula he considered to be trihydrotriiodo-oxybetaproprionic acid, or in other words a triiodine compound of tryptophane, but Harrington has shown that thyroxin is in reality a four-iodine compound of tyrosin, and there is some evidence to suggest that the abnormality in secretion that occurs in primary Graves' disease consists in the production of a substance deficient in iodine. Plummer and his fellow-workers at the Mayo Clinic showed in 1922 that the administration of iodine to patients with exophthalmic goitre produced in most

cases a striking improvement in symptoms. The restlessness, the mental state and the diarrhoea and vomiting, the exophthalmos and the stare were markedly improved and considerable benefit to the cardiac symptoms resulted. Plummer attempts to differentiate the symptoms produced by the dys-thyroidism from those resulting from pure hyperthyroidism, and finds, as was to be expected, that it is the former which are benefited by iodine. Iodine is best administered in the form of Lugol's solution (compound solution of iodine, United States Pharmacopœia), and in a moderate case a dose of 30 minims daily is usually sufficient to control the symptoms attributed to abnormal secretion. Patients in crisis should receive larger doses, 50 to 100 minims daily until the crisis state is under control. If the iodine is vomited it may be given by the rectum, well diluted with normal saline, and that is a good way to give it in post-operative cases. When iodine is administered there is, as I have said, a striking clinical improvement in the patient, and this is accompanied by a drop in the basal metabolic rate, the improvement and the drop reaching their maximum in from ten to fourteen days after the administration is begun. If iodine is continued little further improvement takes place, but on the other hand, although the patient has the usual exacerbations and remissions of the disease, they do not develop an actual state of crisis. When iodine is stopped after it has been administered for a period, however, the patient usually becomes worse. Dysthyroid symptoms reappear and a gastrointestinal crisis may occur two or three weeks after its discontinuance.

There can be no doubt that iodine by itself very seldom, if ever, produces sufficient permanent improvement to justify its continued use as a method of medical treatment. Its greatest value is as a method of pre-operative treatment. By its use in proper doses the crisis can be speedily dealt with, and the patient can be brought into a suitable state for operation in a few weeks.

Further, the use of iodine has very markedly increased the chance of completing the operation in one stage, or at the most in two stages, and it will produce approximately the same degree of improvement that used to be obtained after a polar ligation.

Since the first improvement with iodine always exceeds the improvement seen in subsequent administrations, it is important that it should only be given if possible after consultation between the physician and the surgeon, so that the latter may seize the moment of greatest improvement for operation.

When iodine has been given the thyroid becomes markedly harder to the feel, and microscopically shows considerable colloid storage. Another way in which iodine is of great value is in post-operative treatment. While the post-operative hyperthyroid state is not one which is often encountered, yet when it does occur it is most alarming and used frequently to lead to the death of the patient. Suitable doses of Lugol's solution will nearly always bring it under control, and indeed Lugol's solution should be given routinely after operation.

When all the above factors of safety in the surgical treatment of primary Graves' disease are taken advantage of, the operative mortality in the hands of a surgeon used to the operation should not exceed 3 to 5 per cent., and when cases are submitted to surgery earlier, as they are in America, it should be much less than that. There can, I think, be little doubt that in our present state of knowledge any case which does not get well in the first six months is a surgical case, and it remains for us to consider what form surgery should take.

There can be little doubt that removal of one lobe alone is practically never enough to produce a clinical cure. At least two-thirds of the secreting tissue must be removed in a moderately severe case if the best result is to be obtained, and many so-called surgical failures are really the result of removing too little. The exact amount

to be removed depends on the severity and, as Crile has well put it, if you have as a patient a young married woman with a faithless husband, ailing children, quarrelsome relations, inadequate income and septic tonsils, almost the whole of the thyroid needs removing to effect a cure! The decision whether the operation should be performed in one or two stages depends on the amount of improvement which can be got by medical means before operation. Lugol's solution has made the one-stage operation more frequently possible, and I agree with Wilkie that reaction after a one-stage operation is often less than after a hemithyroidectomy. Nevertheless, I find two-stage operations necessary in a considerable number of cases, and I usually make the decision during the operation, being guided by the way in which the patient stands the first part of it. The question of anæsthesia is still one in which opinions vary. Personally, I find local anæsthesia too temperamentally trying for routine use, and I am so happy in my anæsthetist, Dr. Marston, that I have never yet had a moment's anxiety on this score. After trying varying anæsthetics we now use as a routine avertin, followed by gas oxygen, and that sequence is one which it is hard to imagine could be bettered.

In regard to secondary Graves' disease, that is, as I have pointed out, a local thyroid disease, and its treatment is purely surgical. While border-line cases occur, the typical case is readily distinguished from primary Graves' disease.

In secondary Graves' disease the average age at which a goitre is first noticed is 22, and in primary Graves' disease it is 32. On the other hand, in primary Graves' disease toxic symptoms are present within nine-tenths of a year from noticing a goitre, whereas in secondary Graves' disease the average time before toxic symptoms appear is $14\frac{1}{2}$ years. Exophthalmos is rare in secondary Graves' disease and usual in primary, and the blood-pressure is fre-

quently raised in secondary but not in primary Graves' disease. Usually the thyroid is nodular in secondary Graves' disease, but not always so and, as I have said, border-line cases between the two types occur. Since we look upon secondary Graves' disease as being essentially the result of over-production of normal secretion, it follows that if our explanation of the action of iodine is correct it should not be of value in this type of case. Usually that is so, and indeed some cases of secondary Graves' disease are made much worse by the administration of iodine. In some cases, however, where the changes in the normal thyroid are marked, dysthyroidism occurs and then, of course, iodine is of value. The heart changes in secondary Graves' disease are similar in type to those in the primary condition, but cardiac failure with water-logging, &c., is more apt to occur in secondary Graves' disease. The surgical treatment of secondary Graves' disease is simpler than that of exophthalmic goitre, in that what requires to be done is the removal of the old goitre with a considerable proportion of surrounding thyroid. The risk in these cases depends on the condition of the heart muscle, and as the thyroid origin of many cases of cardiac disorder is frequently overlooked for a long time, the surgeon is not infrequently faced with very bad-risk patients in treating this condition.

It has been my aim to show you in the time at my disposal that at present the treatment of toxic goitre, except the very early stages of primary Graves' disease, is essentially surgical, and I have tried to point out both how the patient may be made safe for surgery and surgery safe for the patient.