An Address ON THE TREATMENT OF EXOPHTHALMIC GOITRE.*

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THE necessity of a close association of medicine and surgery is nowhere more evident than in the treatment of exophthalmic goitre, and this must be my excuse, if an excuse is necessary, for addressing you upon a subject which is so largely medical. It is, indeed, only of recent years that operative treatment of this disease has been regarded as justifiable, for many cases are cured by medical measures, and formerly an operation was a dangerous and hazardous procedure. Even to-day surgery is only safe if combined with careful observation and preliminary treatment. It is therefore accepted by all workers in this field that no operation for exophthalmic goitre should be undertaken until a course of medical treatment has been given; to it the patient may react so well that no operation may be thought necessary, or she may improve to such a degree that the risks of operation are greatly diminished.

To operate upon a patient admitted to the hospital or nursing home the night before is to seek disaster. It may seem unnecessary to stress this point, but I am still occasionally asked to go down to the country to operate upon a case of exophthalmic goitre which I have never seen and which has never been prepared, usually with the added statement that the doctor's partner would like to give the anaesthetic and proposes to administer chloroform. To have acceded to such requests would have raised my mortality figures so high that I should not have dared to address you upon the subject.

A theoretical consideration of the views that have been held as to whether the symptoms are due to dysthyroidism or hyperthyroidism, and how they may best be controlled, would be too lengthy to enter into here, and I propose, therefore, only to discuss with you in detail the methods I now employ, in the belief that in the present state of our knowledge they give the best chance of a satisfactory issue.

Every patient is admitted to the nursing home or hospital for a period of preliminary observation, during which time she may or may not be told that an operation is contemplated. This is a matter which can only be decided in the individual case. Some patients who have had the disease for a long period and have received but little benefit will have heard of the value of operation, and will look forward eagerly to the possibility of obtaining relief thereby. A free discussion of the possibilities of the operation will generally do most to gain their confidence and calm their fears. Many are, however, extremely nervous, and are so easily distressed that it is better not to let them know that an operation is being considered. They can, however, only be kept in ignorance if there are near relatives with whom all the difficulties can be discussed. It is my custom to keep every patient in bed for a week with no treatment other than rest and a modified diet. During this time careful observations are made of the weight and appetite and of the presence of diarrhoea or vomiting. The pulse is carefully observed and the condition of the heart noted. The state of this organ is of the utmost importance in determining the value of surgical treatment. In the minor cases there is usually a rapid and forcible beat with no dilatation, although murmurs which are haemic in character may be present. Later there may be a certain amount of dilatation, but the beat is still regular and forcible. Where the toxæmia has been severe or long continued, auricular fibrillation may be present, and it is necessary to determine whether it can be controlled by preliminary medical treatment. It is important to determine how the patient sleeps at night, and what is the condition of the nervous system. In certain cases an estimation of the basal metabolic rate

may be of considerable value, but it is not my custom to carry out this method of investigation as a routine measure. Not uncommonly it causes a good deal of nervous upset, and so may give a false idea of the general condition. At the end of a week it will be possible accurately to determine what is the patient's general state, and an index will be obtained whereby the surgeon can readily estimate the reaction to preparatory treatment.

At the end of a week treatment is commenced. The patient is still kept wholly at rest in bed, a light diet containing no stimulants is prescribed, and with stimulants must be included meat extracts, tea, and coffee; under modern conditions it is necessary to state that all tobacco must be cut out; otherwise the diet should be full and nourishing. At the same time large quantities of fluid should be given, and it is my own custom to administer daily one pint of rectal saline. This is given at one hour before the time of day at which the operation will ultimately be carried out. Thus, in cases in a private nursing home it is usually administered at 8 a.m., while in hospital it is given at 12.30 p.m. The reason for this time of administration will be shown later.

The careful employment of iodine is now known to be of the greatest value in controlling hyperthyroidism, although its use at one time was the subject of considerable controversy. The balance of experimental evidence seemed to show that the symptoms of exophthalmic goitre were due to hyperthyroidism, and the late Professor Kocher held the view that the administration of iodine would increase the symptoms or might even lead to hyperthyroidism in the case of patients with simple goitre. De Quervain discovered, however, that in certain varieties of exophthalmic goitre the iodine content of the thyroid gland was low, and sometimes, indeed, lower than that found with colloid goitre. Plummer and Boothby found that in certain cases of hyperthyroidism there was an insufficiency of iodine, and hence advocated the administration of some simple form of iodine in the routine treatment of exophthalmic goitre. The value of this drug has since been investigated by many observers, and we have been using it for a long period at the London Hospital. Plummer and Boothby advised the use of Lugol's solution—that is, 5 per cent. iodine and 10 per cent. potassium iodide in water; 10 minims are given daily. All my cases are given 3 minims of this drug three times a day, with results which are often remarkable. The pulse after a day or two not infrequently falls from 120 to 80, the patient becomes much calmer, and the nervous tremor and excitement may almost entirely disappear. Sleep is regained, the weight increases, and intestinal upsets may disappear. These results appear, however, only to be temporary, and my own experience closely agrees with that of Fraser—that if the drug is continued the symptoms tend to return, and that if the dose is increased not only may the beneficial results fail to appear, but the symptoms may even be exaggerated. This is not in accordance with the observations of all surgeons. Jackson states that he could often increase the dosage until 30 or even 40 or 50 minims were administered daily with good results. In all my cases where these large doses were tried the symptoms were increased. If the smaller dose was continued over a period of fourteen days the symptoms also began to return, and it was necessary to stop the drug for a period.

It is also of interest to note that the different varieties of goitre appear to react differently to the various forms of iodine. In my own experience the colloid goitres have been found to react best with the more simple compounds, such as iodide of iron, although these may have to be combined with an intestinal antiseptic. Rapidly increasing or recurring varieties of adenoparenchymatous goitre, on the other hand, fail to react to any form of iodine or iodides, but disappear with thyroid extract. It is hardly necessary to point out that patients suffering from myxoedema fail to improve with the administration of iodine, for they have no thyroid tissue to convert this into thyroxine, and yet it is not uncommon to meet with such cases which have been treated with collosol iodine, with, of course, no benefit. In my experience, exophthalmic goitre improves only with Lugol's solution; iodides have but little effect, and thyroid extract has always seemed

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definitely to increase the hyperthyroidism. In a considerable number of cases where the disease was in a very early stage and the symptoms slight, the improvement with the administration of 3 minims thrice daily has been so great that operation has been postponed and a continuation of the medical treatment tried. In such circumstances the administration of iodine has been reduced to 1 minim three times a day, in the hope that a definite balance could be obtained. With such methods other observers have claimed satisfactory results, but my own experience has rarely been satisfactory. Such patients have made very considerable improvement while in hospital, but on returning to their home life, even if they have not returned to work, there has generally been a gradual relapse, and an operation has had to be undertaken at a later date.

As a general rule the administration of Lugol's solution and the saline is sufficient to relieve all the symptoms, but in certain cases, and especially if there is considerable auricular fibrillation, the condition of the heart will require special treatment. In these severe toxic cases it is always my custom to seek the aid of the cardiologist. Dr. Parkinson has investigated many such by electrocardiograms, and has not uncommonly been able to restore the heart by the use of digitalis and quinidine. It is a fact of very great interest, to which attention has also been drawn by other observers, that a heart which is badly fibrillating may be temporarily restored to normal by the use of these drugs, and may apparently be permanently restored by operative treatment.

Occasionally it may be necessary to give sedative drugs in order to improve the patient's sleep, but as a general rule the nervousness will be so much reduced by the administration of Lugol's solution that quiet and easy sleep is obtained.

Of the value of x-ray treatment as a means of controlling hyperthyroidism I speak with some diffidence, as my experience appears to differ so considerably from that of many x-ray experts, and it is possible that my series includes only more severe or more advanced cases; but in all of my series where it has been tried it has been of little or no value, and has not, as many have claimed, been capable of controlling the hyperthyroidism to any required degree. Some surgeons have objected to its use, as they believed it caused so much fibrosis that if an operation were required later the difficulties would be considerably increased. If this had been my experience I should have regarded it as very strong evidence indeed of the value of x rays in controlling the increased cellular growth of the gland, but I have never found any noticeable change after such treatment, although some of my earlier cases had been so vigorously treated elsewhere that the skin had been extensively burned. The cases in my series include some which have been treated elsewhere and have been sent on to me for operation as this method had failed; some which I have seen very early and have thought not yet suitable for operation; and certain cases where an operation has been performed but insufficient gland has been removed, and the improvement has only been partial. Of the two latter groups I have sent many cases to our x-ray department at the hospital, and they have been returned to me after a time as making no improvement. Cases of carcinoma, on the other hand, have shown an astonishing improvement. I have one or two in my series where the gland has been enlarged, hard, and irregular, where an operation has been performed and the nature of the growth proved, and where there has been secondary glandular involvement. With x-ray treatment the local symptoms have improved enormously, and some of the patients have lived from three to five years. I have come, therefore, to regard the x rays as showing a remarkably selective influence between the overgrowth of a simple hyperthyroidism and a carcinomatous overgrowth.

Selection of the Time of Operation.

A careful choice of the time at which operation is performed is of considerable importance, both as regards the immediate risk and the ultimate prognosis. My cases are very rarely operated upon in the first six months of the disease, for it is in this period that they are most likely to react to medical forms of treatment. Some cases show very

acute symptoms even in this early stage, with rapid loss of weight, the presence of diarrhoea and vomiting, and distinct cardiac changes. An operation performed under such conditions is associated with considerable risk, but careful medical treatment with the use of Lugol's solution will generally lead to a rapid improvement of the symptoms. If the improvement is very marked it will probably be better to postpone the operation for a considerable period, but if, on the other hand, it is only slight, an operation may be considered necessary, while the improvement will be such that it can be safely performed.

All cases of Graves's disease tend to show a periodicity in the severity of their symptoms. Several observers have laid stress upon the fact that the symptoms are severe during the first six months; they then abate for a year or more, to become accentuated again later. There is, in addition, a shorter periodicity, the symptoms varying to a lesser degree almost from week to week. One of these shorter periods of severity is nearly always induced by any disturbance, such as removal to a nursing home or hospital, and it is chiefly for this reason that no operation should ever be performed within a day or two of the patient's entering such an institution. Both the long and the short periods are to-day to a very large extent controlled by the judicious administration of Lugol's solution, and hence it is less necessary to pay so close an attention to the time period. Before the introduction of this method of treatment it was necessary, after the admission of the patient, to watch her carefully until there was a period of abatement, and then to operate. Sometimes it might have been necessary to keep her in hospital three or four weeks before an operation was performed, but nowadays the reaction to preliminary treatment is so definite that it is nearly always possible to operate at the end of a fortnight, the time of operation being selected according to the patient's symptoms rather than to any definite time period.

In more advanced cases secondary changes are not infrequently found in the heart and kidneys, and in some severe examples in my series there has been a profound degree of auricular fibrillation with the signs of cardiac failure. Such cases always carry with them a greater operative risk, but it is remarkable to what a degree their symptoms may be improved by a preliminary course of medical treatment and by the use of Lugol's solution. I have in my series some very interesting cases of women who had severe auricular fibrillation which entirely disappeared with rest and iodine, although it had reacted but little to the previous administration of quinidine. The auricular fibrillation occurred again immediately after operation, but it was again soon controlled, and the patients have since remained well. Although such cases are always more serious, it is well to remember that without operation they will probably progress, and that surgical treatment alone holds out any hope of definite improvement. It is true that even this measure may fail to bring about a complete cure in a seriously disorganized heart, but it will nearly always prevent the condition progressing.

Another fact upon which I have often laid stress is the reaction of these patients to heat, and it is my usual custom, therefore, to refuse to operate in the hotter periods of the summer. Possibly in the future preliminary medical treatment may also be able to overcome this difficulty, but even yet I do not feel safe in this respect, and still refuse to operate in the very hot periods.

Prognosis with Different Types of the Disease.

Clinically three varieties of this disease may be recognized. There is the condition which may occur as the end-result of a colloid goitre. The patient, usually a young girl, has for many years had a simple colloid goitre and then begins to develop the signs of hyperthyroidism. In such cases the thyroid is relatively big and the evidence of hyperthyroidism is often comparatively slight. Such patients react well to treatment, and the operation is not generally associated with much risk. The second type also occurs in young women, but shows evidence of hyperthyroidism from the beginning. It is characterized again by a relatively large thyroid, by marked exophthalmos and vascular changes, but the nervous element is comparatively

slight. These cases are as a rule much improved by preliminary medical treatment. They stand the operation well, and make good immediate post-operative progress. The third variety is seen more often in women at or about the age of the menopause. The thyroid is often smaller, harder, and more irregular. The most characteristic symptoms are seen on the nervous side, these patients being extremely restless, and often showing movements that are almost choreic. Mental symptoms are also very marked. They are generally excitable or melancholy, and sometimes even suicidal. They always stand operation less well than the last two varieties, and the post-operative progress is relatively slow. They also can be much improved by pre-operative treatment, and since the introduction of the more modern methods one is able to carry out operative treatment with a much happier mind.

Choice of Anaesthetic.

In this matter there is considerable divergence of opinion, but all are agreed that chloroform must never be used. It seems to be almost a specific poison. In former times, when the mortality was extremely high, many of these patients died in the preliminary stages of anaesthesia, death being entirely due to the use of chloroform. Many surgeons prefer a local anaesthetic or gas and oxygen. My own preference is for general anaesthesia with such highly nervous patients, and a light ether anaesthesia is always used. To lessen the distress to the patient of the removal to the theatre and of the early stages of induction, ether is administered by the rectum. On the day of the operation the rectal saline is replaced by a mixture of olive oil 3 oz. and pure ether 3 oz. It is for this reason that the saline is always administered three-quarters of an hour before the time at which the operation will ultimately be performed. Generally this amount is sufficient to induce a very satisfactory anaesthesia. The patient is taken into the theatre either completely under or showing a few of the unconscious movements found during the period of induction. The anaesthesia is then continued either with a small quantity of ether on an open mask or by the use of warmed ether vapour. It is usually found when the patient has recovered consciousness that she has had no knowledge whatever of being prepared for the operation, or indeed that the operation has been performed. It must always be remembered, however, that in so inducing anaesthesia the minimum amount must be given, and even in men I have never found it wise to give more than 3 oz. of ether in the rectal mixture.

Method of Operating.

In some of the more serious cases it was the custom to carry out a preliminary ligation of one or more of the arteries before considering resection. I have never performed this operation, but preferred, even before the introduction of Lugol's solution, to watch these cases carefully, and by selecting a time of operation to carry out a partial resection. With the modern methods of preliminary treatment ligation of the arteries alone will probably be abandoned. Wherever possible a considerable portion of the gland should be removed. My usual procedure is to excise one lobe, the isthmus, and the lower portion of the other lobe, and to ligature the vessels of the superior pole of this remaining lobe—that is to say, about three-quarters or rather less of one lobe is left, and even in this the circulation is controlled. Unless the left lobe is the bigger it is usually more convenient to remove the right lobe. If the patient is a bad operative risk, one may have to be content with the removal of only one lobe, but it is almost certain that such an operation, although followed by very considerable improvement, will not lead to a complete cure, and further operative steps will be required later. Some operators prefer to do a more symmetrical operation, which is really only an extensive form of the double wedge-resection which is carried out for colloid goitres. In my opinion this operation is more likely to give rise to haemorrhage, and therefore I prefer the removal as described above. A small drainage tube should always be inserted, and is left *in situ* until any post-operative reaction has abated.

Post-operative Treatment.

When the patient has been returned to bed the ether and olive oil are washed out from the rectum. As soon as consciousness returns the patient is given morphine and atropine, and I have no hesitation in repeating this drug sufficiently to control all post-operative restlessness. In some severe cases it may be necessary to give three or four injections ($\frac{1}{4}$ grain) in the first twenty-four hours. The other important step is to administer large doses of fluid. As soon as the patient is conscious, fluid should be injected by the rectum. I prefer plain water to the usual saline, as I believe it is more easily absorbed. As soon as possible large quantities of fluid should be given by the mouth. With such measures the reaction after operation is often quite slight. The temperature may amount to 99° or 100°, but usually falls again to normal within a few days. The pulse, which immediately before operation may have fallen to 80 or 90, generally goes up again on the day of operation to 120, but rapidly falls, and is often down again to the pre-operative state within three or four days. I have not as a rule found it necessary to administer Lugol's solution within this period, but if there is a more marked reaction, very considerable benefit may be gained by its administration, and there is no doubt that it is a very useful aid in controlling post-operative hyperthyroidism. During this important post-operative stage the patients should always be kept as quiet as possible, and in hospital wards it is our custom to have them screened off from the rest of the ward, and also kept as cool as possible, electric fans being freely utilized.

Operative Results.

In spite of every care in the preparation there is still a very definite mortality which will vary according to the surgeon's method of selecting his cases for treatment. Advanced cases, where there are already secondary changes in the heart and other viscera, will stand operation somewhat badly, and hence, if a surgeon is prepared to attempt the cure of these serious and distressing cases, his operative mortality will be relatively high. Several series have been recorded in which the mortality was reduced to some 3 or 4 per cent., and Pemberton has published a group of over 1,000 cases where operative mortality was under 1 per cent. The usually accepted risk is about 5 per cent. In my own group there were 189 cases with 10 deaths, a mortality of just over 5 per cent., although it is less in the more recent cases. It has always been my custom to offer the help of operative treatment to very advanced cases in which there is no other hope of cure. With the use of Lugol's solution the outlook is greatly improved, and the mortality has been much reduced since its introduction. My series included 170 females and 19 males, approximately 1 in 10 males. In 1923, when writing on the same subject, I quoted the experience of Murray, that in recent years the proportion of males had been increasing, and stated that up to that time my experience had not been in accord with this. Since then, however, there has been a definite tendency in this direction, so that in the last 41 cases there have been 8 males, a ratio of 1 in 5.

In estimating the value of any operative procedure the end-results, and the progress towards such results, are of even more importance than the immediate mortality. Of my 189 cases 7 must be deducted as having been performed for too short a period to estimate the end-results of treatment. Of the remaining 182, 9 died as the result of operation, leaving 173 for investigation of their after-results. Of these, 95 (54.8 per cent.) are completely cured. They have no physical signs and no symptoms of their disease. The 95 have been observed for the following periods: for five years 47, for four years 12, for three years 8, for two years 14, and for one to two years 14. Forty-six (that is, 26.5 per cent.) are sufficiently cured to be able to live a normal life, performing their usual duties, and in the majority of cases earning their own living. They still, however, have a mild degree of tremor or some slight exophthalmos, or even a pulse which is easily increased in rapidity. Of the total, therefore, 81 per cent. have been converted from a condition of invalidism to people who are able to live normal lives. Some of the forty-six

who still have symptoms have been operated upon at a relatively short period, and will almost certainly continue to improve until they are completely cured. Three of the cases have developed a considerable hypertrophy of the remaining portion of the thyroid, and have had little or no improvement of their symptoms. It is probable that they may yet be improved by further operation, which is now contemplated. In addition to these, 3 others, who had apparently passed to a state of complete cure, relapsed owing to some severe mental stress, 2 of them as a result of having been exposed to air raids. These have since improved so much under medical treatment that no operation has been contemplated, although they still have some evidence of the disease; 8 have died since operation—one from pneumonia; one during a confinement; 2 six and four years respectively after the operation, apparently from conditions not connected with the thyroid; one developed carcinoma of the skin owing to an x-ray burn and has since died from this; 2 were said to have died from heart disease, which must be regarded as being dependent upon their Graves's disease; one developed diabetes and died, and although all symptoms of Graves's had disappeared there is so close a relationship between these two conditions that this fatality must be included as a post-operative possibility. In addition to the patient who died from diabetes, one other has diabetes, which is controlled by medical treatment, and she has no symptoms of exophthalmic goitre. She has therefore been included among the group who are relieved. Nineteen have been lost sight of.

These results may be tabulated thus:

Quite cured	...	...	...	...	...	94
Greatly relieved	...	...	...	...	...	46
No better	...	...	...	...	...	3
Died after operation	...	...	...	...	...	9
Late deaths	...	...	...	...	...	8
Lost	...	...	...	...	...	19
Relapsed	...	...	...	...	...	3

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It is justifiable to claim, therefore, that as a result of operative treatment there will be an immediate mortality of about 5 per cent., a late mortality of under 2 per cent., a certainty of complete cure in about 55 per cent., and of sufficient relief for the patients to earn their own living in comfort in 81 per cent.—results which are unlikely to be obtained by medical treatment alone.

It is important, however, to realize that there is not an immediate cure as a result of operation. I have on several occasions pointed out that the post-operative progress passes through several stages, which may be classified as follows:

1. *The Stage of Reaction.*—This is the dangerous post-operative period, and it lasts from three to four days after operation, the symptoms in the majority of cases being due to a definite post-operative hyperthyroidism. With modern methods of operation it is much less in evidence. If the symptoms become serious they can generally be controlled by the administration of Lugol's solution, of large quantities of fluid, and of morphine.

2. *The Stage of Primary Improvement.*—Within a fortnight from operation a great improvement is nearly always manifest. Many patients before leaving hospital have a normal pulse with no tremor; they are eating and sleeping well, the exophthalmos may be much reduced, and the improvement from their condition on admission is often startling.

3. *The Stage of Primary Relapse.*—Nearly always on returning to home conditions there is a disappointing return of the symptoms. The relapse is slight in degree, but it is because of its presence that a rather prolonged convalescence is required, and that the patients must be carefully watched and treated for a considerable period. As a general rule, it does not last longer than four to six weeks, but if the case has been so severe that it has only been possible to remove a relatively small portion of the thyroid, the patient may permanently remain in this stage, and although showing improvement will not pass to a stage of complete cure. This is not uncommonly a difficulty with such cases. It is evident that further operation is required to bring about a cure, but the patient may be so much relieved that she refuses to go through the discomfort of a second operation.

4. *The Stage of Apparent Cure.*—After a few months these patients lose all their symptoms. There is no enlargement of the thyroid, all nervousness disappears, the pulse is normal, and the exophthalmos slowly disappears. The patients appear to be absolutely cured, and if everything is satisfactory they will pass on to a state where they are absolutely cured. It is only by having watched many cases that one realizes that during this period any severe mental shock or upset may be followed by an enlargement of the remaining portion of the thyroid and by recurrence of the symptoms. It is very difficult to estimate how long this period lasts, but it would appear to persist for one or two years. At the end of this time the cure is apparently complete, for not only are the patients free from all symptoms, but they seem to be able to face all normal disturbances and upsets with no fear of a recurrence of the symptoms.

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A Lecture

ON

THE USE OF HYPERTONIC SOLUTIONS IN THE TREATMENT OF INCREASED INTRACRANIAL PRESSURE.*

BY

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Two cardinal facts about the skull and its contents form the basis of a true understanding of the pathology of the intracranial pressure. The skull in the adult is a rigid case which is incapable of expansion, and the total volume of the intracranial contents is therefore constant. These contents may for practical purposes be regarded as three—the brain, the cerebro-spinal fluid, and the blood in the blood vessels. Since their total volume is constant, an increase in the volume of any one of them can only occur at the expense of the volumes of one or both of the others. For example, if the brain becomes enlarged by the growth of a tumour there must necessarily be a corresponding decrease in the volume of the blood or of the cerebro-spinal fluid, or of both. Such readjustments can only occur to a very limited extent without raising the intracranial pressure.

The most obvious way to reduce raised intracranial pressure is to abolish in part the rigidity of the skull—in other words, to perform a decompressive operation. This was till recently the only method available, and it is still the method of election in certain circumstances. There are, however, a number of conditions associated with increased intracranial pressure in the treatment of which such a serious operation is unjustifiable, and others again in which it is to be avoided if possible. My present object is to describe another method of lowering the intracranial pressure which has many therapeutic applications, and which can be used sometimes as a substitute for, and sometimes as an adjuvant to, craniectomy.

The Physiological Action of Hypertonic Solutions.

We owe to Weed the discovery that hypertonic solutions can be used to lower the intracranial pressure. Weed

* Delivered to the South Middlesex Division of the British Medical Association.