

THE TREATMENT OF THYROTOXICOSIS

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Introduction

This is a good moment to describe the treatment of thyrotoxicosis. For 15 years new ideas have jostled for recognition and controversy has raged. Now throughout the world there is a salutary pause from argument and, apart from minor details of technique, general agreement reigns. We stand momentarily poised, like a statue of an athlete, awaiting the signal for the next advance, which will inevitably cause fresh conflict.

There are now three definitive treatments of thyrotoxicosis, by partial thyroidectomy, anti-thyroid drugs and radio-active iodine.

Partial thyroidectomy remains, in *ideal circumstances*, the best treatment in most cases. By 'ideal circumstances' I mean circumstances in which experience in diagnosis and skill in treatment are of the highest order. Thyroidectomy is an operation demanding (if the best results are to be obtained with safety, permanence and the minimum of discomfort to the patient), the maximum of skill and experience of the surgeon, perfect co-operation with the physician and perfection of nursing. In such circumstances the patient is returned to health more rapidly and more certainly than by treatment with anti-thyroid drugs or by radio-active iodine. The exceptions to this rule are few: the young girl, the patient with severe cardiac disease or other coincident disorder which increases the risk of surgery or general anaesthesia, and the elderly patient with little or no thyroid enlargement.

Treatment with radio-active iodine has been practised for nearly 20 years. There is no doubt of its efficacy, but three factors have prevented its general use. In the first place it can only be used with efficiency and safety in special units equipped with expensive apparatus and manned by specially trained clinicians and biophysicists. In the second place it is still impossible to gauge with accuracy the dose required. Whatever method of calculation is used (and such methods vary from the use of complicated formulae in some hospitals to the roughest guess-work in others), the results are similar—some 60% to 70% 'one-dose cures',

the remaining 30% to 40% of patients requiring further treatment or lapsing into permanent hypothyroidism. In the third place we are not yet in a position to discount the possible sinister results many years later. For this reason the majority of responsible physicians refuse the treatment to patients under the age of 45 years, unless other considerations make surgery inadvisable. The most important of these considerations are severe cardiac disease and, occasionally, thyrotoxicosis recurrent after previous operation. I am chary of admitting fear of operation as an indication for treatment with radio-iodine, preferring to treat the fearful patient by antithyroid drugs until, as usually happens, his fear of surgery is eliminated. Nevertheless, it seems probable that the fear of carcinogenesis and leukaemia will one day prove to be illusory and treatment with radio-iodine will become general for younger patients.

The Use of Antithyroid Drugs

It is only fair to say that antithyroid drugs have not fulfilled the expectation of early enthusiasts. When thiourea was first introduced optimists foretold the end of thyroidectomy for Graves's disease. Gradually this view has been abandoned. Every patient with thyrotoxicosis, whether his thyroid be diffusely enlarged or nodular, can be relieved of his symptoms with antithyroid drugs, usually in from two to six weeks, but even if the treatment be continued for a year relapse is to be expected.

Although in older patients relapse after treatment with antithyroid drugs is almost inevitable, these may be worthy of prolonged trial in young girls. Some will remember that, before thyroidectomy attained its present high level of safety, and when, therefore, it was avoided whenever possible, patients occasionally recovered after medical treatment. This consisted of prolonged rest in bed, deep sedation, attention to the general health and an attempt to solve domestic, social and psychological troubles if these were present. Sometimes the patients were given iodine in various forms, each with its devoted advocates, and by

various unnecessarily complicated systems of dosage. Those who recovered were usually young girls with thyroids diffusely and only slightly enlarged, with a mild degree of thyrotoxicosis and often an apparent emotional 'cause' of a reversible kind. It is this kind of patient who sometimes makes a permanent recovery when treated with antithyroid drugs and one may be allowed to suspect that one has controlled the disease while a spontaneous recovery was on the way. Very rarely, too, a diffuse goitre in a middle-aged woman may become smaller during treatment, instead of remaining constant or even tending to increase, as is usual during treatment with antithyroid drugs. In such a way there may be hope of a permanent cure. In places remote from the opportunity of skilled surgery the permanent use of antithyroid drugs may be the best treatment for the majority of patients.

The Antithyroid Drugs

A wide choice of antithyroid drugs is available, but in most special clinics the choice now lies between carbimazole ('Neomercazole') and potassium perchlorate. The earlier drugs, thiourea and thiouracil, gave place long ago to methyl and propyl thiouracil, which, though an improvement on their predecessors, still carried with them a 10% risk of toxic reactions. With carbimazole and potassium perchlorate such reactions are very rare and usually of little consequence. The former is a well-tried drug of great reliability. The latter has had a shorter trial; it may prove to be equally reliable.

Carbimazole was introduced by Lawson, Rimington and Searle.³ Its toxic effects were fully described by Greene and Morgan,² who showed that these were less than those of the antithyroid drugs previously in use. Serious effects upon the blood occurred in only seven out of 435 patients treated with carbimazole (1.6%), but in 160 out of 6,567 (2.4%) of those treated with methyl thiouracil. Rashes occurred about twice as often with the latter drug. Potassium perchlorate has been used in far fewer patients, and it would be premature to draw definite conclusions about its toxicity. Wayne⁴ and Crooks and Wayne¹ have reported that in a dosage of 1,500 mg. or more the liability of potassium perchlorate to produce toxic reactions is not statistically less than that of the older drugs. With doses of 600 mg. to 1,000 mg. the toxicity was apparently less. In common with the group with which I work, Wayne settled for a dose of 1,000 mg. daily. His figures are too small for any conclusions to be drawn, but his experience 'suggests that potassium perchlorate is less likely to give rise to skin rashes or blood

dyscrasias in doses which act as quickly as the conventional therapeutic doses of methylthiouracil and carbimazole'. Our own experience, gathered from a series even smaller than Wayne's, is that potassium perchlorate in effective doses is as toxic as carbimazole, which means, in effect, that neither is sufficiently toxic to give rise to anxiety. We are not satisfied that the effects of potassium perchlorate are as predictable as those of carbimazole. On the other hand, it is much cheaper. To treat one patient with 30 mg. a day of carbimazole for one month costs 16s. 2d. A course of 1,000 mg. a day of potassium perchlorate costs only 2s. 7d., and further experience may show that it is equally effective and that our preliminary doubts are unjustified.

Carbimazole or potassium perchlorate is given almost always in preparation for thyroidectomy, from which the antithyroid drugs have subtracted all its terrors. Thyrotoxicosis is controlled in the out-patient department, the patient, except when very severely ill, remaining at work. When the signs and symptoms have been completely, or almost completely, relieved admission is arranged for the near future. When carbimazole has been used it is wise to give iodine for a fortnight before the date of operation in order to facilitate the surgeon's work, the carbimazole being stopped a week before operation. The traditional prescription for iodine is Lugol's solution, 5 minims twice daily in milk, but Lugol's solution has no real virtue of its own and iodine in any form is equally effective in making the gland less friable and less liable to bleed. If potassium perchlorate has been used, the administration of iodine is unnecessary and ineffective. The operation, in uncomplicated cases, is usually performed on the day after admission and the patient is usually fit to get up on the next day and to leave hospital in seven to 10 days.

If, in the special circumstances already described, it is decided to use an antithyroid drug as the definitive treatment, the full dose (10 mg. t.d.s. of carbimazole or 1,000 mg. a day of potassium perchlorate) is continued until the signs and symptoms of thyrotoxicosis have been eliminated. The dose is then gradually reduced to that which keeps the patient euthyroid and continued for at least a year. The patient thereafter is kept under surveillance. Unfortunately, relapse usually occurs within a few months or years. Further treatment produces another remission, but one can be sure that if relapse occurs once it will occur again. It is quite unjustifiable thus to play 'cat and mouse' with the patient and a single relapse after antithyroid treatment should be considered an indication for thyroidectomy in the young and for thyroidectomy or radio-iodine in the middle-

aged or old, provided that the facilities are available.

Antithyroid drugs are occasionally used as a preparation for treatment with radio-iodine, especially in cases of nodular goitre. It has been stated that such treatment 'evens out' the activity of the gland and makes the calculation of the dose more accurate. I have not observed any improvement in the results when this method has been used, but carbimazole may be useful in temporarily controlling thyrotoxicosis should there be any inevitable delay before radio-iodine is given. It may also be given temporarily after radio-iodine to control thyrotoxicosis during the inevitable latent period before clinical improvement begins.

Complications of Antithyroid Treatment

True complications very rarely occur during treatment with carbimazole or potassium perchlorate. In Greene and Morgan's series, in which carbimazole was used, they numbered 3.4%, with no deaths. In Wayne's series the complications with carbimazole amounted to 8.2% and with potassium perchlorate 4.8%; he mentions no deaths. Agranulocytosis has been a very rare complication. Combining the two series quoted, it has occurred five times in 520 patients treated with carbimazole and once in 250 patients treated with potassium perchlorate. It is the only true complication to be feared, though skin rashes, nausea and drug fever may be an occasional nuisance.

Enlargement of the thyroid and myxoedema may occur during treatment. These are not true complications, but the result of too much treatment. The drug should be stopped and, when the

effects of overdosage have subsided, administered again at a lower dosage.

General Treatment

The value of surgery, radio-iodine and carbimazole in the treatment of the overactive gland should not be allowed to dwarf the importance of treating the person of the patient. Heredity, geography or an unknown agent may have loaded the gun; another has pulled the trigger. We can probably do little, if anything, about the former. The latter may be remediable. It may be the need for rest, mental or physical, for a change in environment, or a change of occupation. The general health of the patient is too frequently forgotten and too much reliance placed on methods of treatment designed to influence the function of but one small part of his anatomy, albeit the one most at fault.

Summary

The antithyroid drugs of choice are carbimazole ('Neomercazole') and potassium perchlorate. The toxicity of the latter may be slightly less, but of both it is very slight. Their main use is in the preparation of patients for thyroidectomy, though in a few selected patients or in unfavourable circumstances they may be used as the definitive treatment of thyrotoxicosis.

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