THIOURACIL AND ITS DERIVATIVES IN THE ROUTINE TREATMENT OF THYROTOXICOSIS*

BY

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Five years have elapsed since the introduction of thiouracil and its derivatives into the treatment of thyrotoxicosis (Astwood, 1943), and the time now seems ripe to attempt an assessment of their efficacy and safety in practical therapeutics. Such an assessment can be made with certainty as regards the immediate effects of this therapy, with a high degree of probability regarding its results over several years, but, because of the uncertainty surrounding the natural duration of the disease itself, only provisionally in respect of the ultimate prognosis. For convenience of discussion it is proposed first to consider the relative value of this treatment when no contraindication such as idiosyncrasy precludes its use, next to define the dangers which attend its employment, and finally to outline a scheme of treatment applicable under the conditions of general practice.

It is now established beyond any reasonable doubt that by means of thiouracil the manifestations of thyrotoxicosis can rapidly and effectively be brought under control. Interest in regard to this initial phase of treatment has moved to the consideration of factors modifying the response of the patient to thiouracil therapy. There is no doubt that different patients vary widely in the speed of their response, although the great majority are controlled within a month or six weeks. As a general rule the more severe the case the more dramatic the response, so that, although many cases are too severe for any other form of initial treatment, one can say that there are no cases too severe for thiouracil therapy. To this fortunate fact may be attributed the virtual disappearance of deaths from that highly fatal exacerbation of thyrotoxicosis, the thyroid crisis.

There remain, however, a few cases which react so slowly as to be relatively resistant. These include some patients with nodular goitres and those previously treated with iodine. Premedication with iodine can cause a temporary but well-marked resistance, so that if it is desired to give thiouracil to a patient already under treatment with iodine the latter should be omitted for a month before the new therapy is instituted. Curiously enough, this inhibitory effect of iodine does not occur when it is given to patients already under control by thiouracil, and surgeons using thiouracil as a pre-operative measure take advantage of this fact to make the thyroid gland turgid with colloid, less vascular, and so more easy to handle at operation.

Dosage

The other knowledge that has emerged from experience in the initial treatment of the disease is that unnecessarily large doses of thiouracil have been used in the past. Origin-

ally 1 g. daily was employed. Later the dose was reduced to 600 mg. Now we find (Trotter and Himsworth, 1948) that an equally good response is obtained by using a total dose of 200 mg. of methyl thiouracil a day.

Once the patient's symptoms are brought under control the stage of maintenance treatment is reached. From the early days of thiouracil therapy it has been appreciated that if the drug is omitted as soon as control has been achieved relapse soon follows (Astwood, 1943; Himsworth, 1944). But the dose required to maintain control is far less than is required for its institution—25, 50, or, at most, 100 mg. daily will suffice save in exceptional cases, and more will sooner or later produce myxoedema. The aim should be to give the minimum dose of thiouracil required to maintain the weight gained, the resting pulse rate at 80 or thereabouts, and the symptoms in abeyance. Should the patient's requirements fall faster than reduction of dosage myxoedema will arise, and this will quickly be brought to the physician's notice by the patient's complaints of inertia and tiredness, and by the appearance of puffiness of the face.

The effect of thiouracil upon certain special features of thyrotoxicosis, such as the eye signs, the goitre, and the occasional complication of auricular fibrillation, can now be stated with some assurance (Himsworth *et al.*, 1947).

A distinction must be drawn between exophthalmos—genuine protrusion of the eyeball—and lid retraction (Pochin, 1937–8). Although it is customary to speak of exophthalmic goitre, only about one-third of the cases of thyrotoxicosis with diffuse goitre, and less than one-tenth of those with nodular goitre, have true exophthalmos. In the majority of cases the appearance of exophthalmos is an optical illusion dependent upon retraction of the upper lid, and, although most cases of true exophthalmos have lid retraction as well, it is to this that the staring appearance of the eyes is largely due. As a practical clinical rule it can be said that true exophthalmos is revealed by visible sclera below the cornea, and lid retraction by visible sclera above the cornea. The effects of thiouracil therapy on these two ocular components are exactly the same as the effects of thyroidectomy. It does not reduce true exophthalmos, and indeed, like surgery, may lead to its increase. It removes lid retraction in about two-thirds of the cases and reduces its degree in practically all: again, as with surgical treatment, this beneficial result may not be fully achieved until one to two years after treatment is begun.

In patients receiving thiouracil the goitre may enlarge, diminish, or remain unchanged. Enlargement is due to overdosage. Slight or moderate diminution in the size of the gland occurs in most cases with toxic diffuse goitre. Disappearance of the goitre has as yet been observed in less than 10% of such cases, and then only after two or

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more years of treatment. It is possible that with longer periods of observation a larger proportion of cases will behave in this way; and in this connexion it should be noted that the gland may continue to diminish after it has been judged permissible to stop thiouracil treatment. Nodular goitres, so far as is known, remain unchanged.

Auricular fibrillation complicating thyrotoxicosis is susceptible to thiouracil therapy. If the arrhythmia is intermittent it usually disappears completely with control of the thyrotoxicosis. If persistent it may so disappear, but, should it not, the rhythm can be brought to normal with quinidine after the thyrotoxicosis has been controlled. It then usually remains regular.

Chances of Cure

The question now arises, Is it possible to cure thyrotoxicosis with a course of thiouracil therapy? It has already been mentioned that if thiouracil is stopped after the three to four weeks' treatment required to bring the disease under control then the patient relapses to his original state in about the same time. It was soon noted, however, that if control was maintained for longer periods the patient took correspondingly longer to relapse, and it became evident that some patients showed no signs of relapsing at all. It is as yet too early to talk of permanent cures in the sense that the patient is rid of his thyrotoxicosis for life, but the evidence already available suggests that remissions which show every indication of being established occur in a reasonable proportion of the cases treated solely with thiouracil (Himsworth, Morgans, and Trotter, 1947; Trotter and Himsworth, 1948). Our early results bearing on this point were vitiated by stopping treatment too soon. We had not then appreciated that treatment must be continued for months after the condition has been brought thoroughly under control. In those of our cases which have had a remission lasting over two years since thiouracil was stopped the average duration of thiouracil treatment was 15 months $\pm$ 6.3. Judging by the experience with 22 patients who have been followed up since they were given a course of thiouracil three years or more ago there is a steady decline in the number requiring thiouracil until, after 2½ years, only about one-third of the total need it. These consist of patients who have continued to need the drug and those who, having stopped its use, began to show signs of thyrotoxicosis and need to start it again. All the patients in the group, however, are well and at work irrespective of whether they are taking thiouracil or not. Whether with further observation some of those who have relapsed will, after more treatment, join the group who have achieved what promises to be either a cure or, at least, a prolonged remission remains to be seen. At present it can be said that a patient starting thiouracil treatment has about a 3 to 1 chance of securing an apparently permanent remission after about 9 to 21 months of treatment.

Mechanism of Remission

How thiouracil produces an apparently permanent remission is still obscure—as obscure as how subtotal thyroidectomy does the same thing. It is probable that both treatments affect the body in the same way, for both reduce the output of thyroid hormone, one chemically and the other mechanically. What is apparent from the experience with thiouracil is that to secure a remission the production of this hormone must be restrained within normal limits for a considerable period. This suggests two possible explanations (Trotter and Himsworth, 1948). The first is that thyrotoxicosis is a condition of limited duration tending to spontaneous cure in a matter of months or a few years, and that thiouracil and thyroidectomy simply tide the

patient over until a spontaneous remission occurs. Observation on cases collected before surgical treatment was widely available (Murray, 1902; Mackenzie, 1905) lend some support to this idea. The second is that these measures break a vicious circle. Ordinarily, thyroid activity is adjusted by the anterior pituitary gland to maintain a rate of metabolism which we call normal, increased output of the thyroid hormone inhibiting the anterior pituitary gland and so indirectly retarding thyroid activity, diminished output causing increased pituitary activity and secondary stimulation of the thyroid. The patient with thyrotoxicosis maintains her metabolism at higher levels than this. It is possible that when her heightened metabolism is reduced to normal by curtailing the production of thyroid hormone, and is maintained at the normal level for a sufficiently long time, the activity of the influences controlling thyroid activity may become adjusted to work at this new and normal level of metabolism and so permit a cure to be established. This latter suggestion would explain the observation that the duration of remissions after thiouracil lengthens with the duration of the antecedent therapy, and would be in accord with the hypothesis that exophthalmic goitre proper is essentially due to overactivity of the anterior pituitary gland, the exophthalmos being a direct expression of this and the thyroid hyperfunction a secondary effect.

Dangers of Thiouracil Therapy

Attention can now be turned to the dangers of thiouracil therapy. In doing this a clear distinction should be drawn between the effects of overdosage (that is, those effects which can be produced in any person by giving too much of the drug) and idiosyncrasy (those effects occurring in a minority of patients who are inexplicably susceptible to its action).

Overdosage.—The two main manifestations of overdosage—increase in size of the goitre and myxoedema—have already been mentioned. They are easy to recognize and are speedily remedied by omitting treatment, but should not occur. A common manifestation of its action that might be mistaken for overdosage may conveniently be mentioned here. In many patients the level of white cells in the blood is lower after a week or so of treatment than it was at the beginning. So long as the total count is not below 3,000 per c.mm., and the polymorphonuclear cells constitute 50% of the total, this fall can be disregarded.

Idiosyncrasy.—Manifestations of idiosyncrasy occur in about 10% of patients (Moore, 1946), but not all are an indication for abandoning this form of treatment. They rarely appear before the seventh day and 80% occur within six weeks of starting thiouracil. The majority of sensitive patients are thus weeded out in the period during which they are under close observation. The only common toxic effects are drug fever and skin rashes. Provided these are not accompanied by a significant fall in the polymorphonuclear cells of the blood, treatment should continue without interruption. The fever usually occurs at the tenth day, and lasts two or three days. If thiouracil is omitted it subsides, only to return when the drug is restarted; if thiouracil is continued it disappears permanently. Other, but uncommon, reactions which are usually transient and do not necessitate cessation of therapy are enlargement of the lymphatic glands, spleen, and salivary glands, and joint swellings. These manifestations of sensitivity are all relatively minor matters; but there is one manifestation—agranulocytosis—which is serious, and as the danger from this has been heavily stressed it is necessary to review the subject in the light of more mature experience.

Agranulocytosis.—Agranulocytosis occurred in 207 out of 9,281 cases under treatment with thiouracil—that is, in about 2% of all cases (Moore, 1946). Of these one-quarter died. In assessing these results one must remember that those 9,000-odd cases were the first to be treated with thiouracil, when heavy doses were employed and physicians were only just beginning to

learn how to use the drug. It is probable that a second survey now might reveal a lower incidence. The second point to remember is that at the time when these cases were under treatment penicillin was not available to all clinics participating in the survey, and that if it had been the mortality rate would have been much lower. As agranulocytosis is the only cause of death in thiouracil therapy this is a matter of some importance when comparisons are being made with other methods of treatment. It now seems clear that disappearance of the polymorphonuclear cells from the blood causes no ill effects unless infection supervenes. Stop the drug, abolish the infection with penicillin, and in the space of a week or ten days granulocytes will return to the blood and recovery occur. The whole problem is one of early diagnosis. If this could be ensured it is probable that the majority of cases, if not all, would recover. In an attempt to detect cases in the early stages Dr. M. E. Morgans, in my unit, has carried out frequent blood counts, including Arneht counts, to detect any inflow of immature cells. We have come to the conclusion that such precautions are worse than useless: useless because agranulocytosis develops like a bolt from the blue, and sometimes within two or three days of finding a normal blood count; worse than useless because a normal count may impart a quite unjustifiable sense of security. The only real safeguard is to ensure that the patient thoroughly understands that on the advent of fever or sore throat he must immediately inform his medical attendant and stop taking thiouracil. On receipt of such information the doctor, whatever the hour, should arrange for a blood examination, and if this reveals few or no polymorphonuclear cells he should start penicillin therapy in full doses at once. Few physicians several years removed from qualification would care to trust to the accuracy of blood counts performed by themselves. But we can all recognize a polymorphonuclear cell in a stained blood smear and so tell whether agranulocytosis is present or not. To make such smears is a simple matter, and if the physician is prepared to do this or can arrange for it to be done he can undertake thiouracil therapy with few qualms. When, however, agranulocytosis has once developed, treatment with thiouracil should be abandoned and recourse be had to surgery.

Malignant Changes.—The question has also been raised whether thiouracil might not induce malignant changes in the thyroid. Malignant changes have been produced in animals by using large doses of thiourea over several years. But such experiments are not comparable, either in dosage or in relative duration, to therapy in man. Sooner or later, however, it is inevitable that a case of carcinoma of the thyroid will be misdiagnosed as a benign toxic goitre and treated with thiouracil. When one considers the thousands of patients treated in this way, and the heavy dosages employed previously, it is significant that, so far as I am aware, no convincing case of carcinoma of the thyroid in a patient treated with thiouracil has as yet been reported.

It will be noted that no mention has been made of the relative toxicity of the different derivatives of thiouracil. Between the three in common use at present—thiouracil, methyl thiouracil, and propyl thiouracil—there is, according to our experience on man, little to choose (Morgans, 1947). The majority of our cases have been treated with methyl thiouracil.

Comparison with Surgery

The final question in assessing the value of this new therapy is that of its relative safety and efficacy in comparison with subtotal thyroidectomy. First the relative safety of the two methods may be considered. The death rate ascribable to thiouracil is entirely due to the complication of agranulocytosis. Even in the first series of cases treated it amounted to no more than 0.4 to 0.5%. The general mortality rate from thyroidectomy is unknown. Superb surgeons, operating with trained teams in special clinics, claim to have reached figures which approach those obtained in the early days of thiouracil treatment. It is probable that the mortality rate in the best general hospitals, both in this country and abroad, is not far below 2%. In this country in general it is certainly considerably higher. So, even if all those affected by agranulocytosis

were to die, the mortality rate over the country as a whole for cases treated with thiouracil would still be considerably less than for those treated surgically. And there is another factor to be taken into account in this connexion—the cases judged to be too severe for surgery. Such may be few with a highly skilled surgeon, but in this group the mortality rate is high. No cases are too severe for thiouracil. From the standpoint of safety as a routine treatment there can therefore be little doubt that thiouracil treatment is, in the absence of certain special complications mentioned below, the treatment of choice.

The next point to be considered is the relative efficacy of the two methods in the control of toxic symptoms. It can be answered in a sentence. Judged by any criteria—abolition of symptoms, gain in weight, capacity for work—thiouracil will do anything that the best surgery can. Lastly there remains the question of their respective abilities to promote a cure. We know that by means of surgery the majority of cases of thyrotoxicosis receive lasting benefit. It is still too early to judge the permanency of the benefits of thiouracil treatment. What can be said now, however, is that two-thirds of the patients so treated may expect to achieve what has every appearance of being a permanent remission, but that it is as yet impossible to distinguish on first attendance those who will from those who will not respond so favourably. In view of this promising experience, the safety of thiouracil treatment, and its efficacy in controlling thyrotoxicosis it seems permissible to suggest that, with the few exceptions mentioned later, all cases should first be given a full course of medical treatment and subsequent therapy determined by the results of this. The comparison now resolves itself into matters of circumstance. Is it preferable to enter on a long course of thiouracil treatment or to take the risk of operation at the start and thus curtail the period of medical supervision? Is the goitre so disfiguring as to be a significant factor in the patient's life? Can the patient be trusted to observe instructions? These are questions which must be answered in the light of the facilities available and the patient's temperament, and the only person who can answer them is the patient's medical attendant.

A Scheme for the Routine Use of Thiouracil

The foregoing considerations can now be summarized in a scheme for routine treatment with thiouracil.

When a patient is obviously thyrotoxic, put her to bed, give appropriate sedatives, and start thiouracil at once in doses of 100 mg. twice daily. This will remove all danger of the condition getting worse and allow ample time for further consideration. If, on the other hand, the case appears mild and the diagnosis seems doubtful, put the patient to bed, prescribe sedatives, and observe the effect. If still in doubt after several days of observation, then nothing but an estimation of the basal metabolic rate will settle the diagnosis.

Examine the goitre carefully. Obtain, if possible, antero-posterior and lateral radiographs of the trachea. If tracheal compression is present or there is any suspicion of malignancy, surgical measures are indicated. Similarly, if the goitre is wedged in the upper aperture of the thorax or is large and retrosternal, surgery is advisable. In the absence of such complications proceed with thiouracil treatment.

Continue treatment with 200 mg. daily until the weight is rising, the pulse is slower, and the symptoms of thyrotoxicosis are obviously disappearing. Determinations of the basal metabolic rate are unnecessary save for diagnostic purposes. A close watch should be kept on the temperature, and if this rises or any toxic symptoms appear the blood should be examined for agranulocytosis. Routine

blood counts are, however, both unnecessary and useless. Judge the improvement by clinical evidence. When improvement is apparent, allow the patient to get up; when obvious—and this will usually take about a month to six weeks—reduce the dose to 50 mg. twice a day.

The stage of maintenance therapy has now been reached. As soon as the rising weight curve begins to level off, or if there is any suggestion of myxoedema, reduce the dose to 50 mg. a day. This will suffice in the majority of cases, but if it does not, and the weight begins to fall and slight symptoms return, raise the dose again to 50 mg. twice a day. Having determined the appropriate dose, maintain it at this level for at least twelve months. Keep a close watch for the sudden appearance of lethargy and puffiness of the face, which are the first signs of myxoedema, and if these appear reduce the dose. If after nine, twelve, or fifteen months the condition is satisfactory, give 50 mg. on alternate days for three to six months. If the condition remains satisfactory, treatment can be suspended. When in doubt, continue treatment.

The frequency of visits to the patient depends upon the accuracy with which information can be obtained of her condition. Assuming that reasonably reliable information can be obtained, the patient should be seen daily during the initial period, less frequently in the second month, at weekly or fortnightly intervals in the third, and thereafter she need not be seen more often than once a month, or even, towards the end of the maintenance period, once every two or three months. After cessation of treatment the patient should attend at three-monthly intervals for the first year. These infrequent visits to a patient undergoing a treatment which is potentially, if only slightly, dangerous are suggested on the understanding that the physician is confident that the patient will at once report any untoward event and that immediate arrangements can be made for the simple investigations necessary to detect agranulocytosis. It cannot be too strongly emphasized that every patient must understand that on the appearance of fever or a sore throat thiouracil must be omitted and the doctor informed at once, and that the blood must be examined for granulocytes immediately. Should they be few or absent, penicillin in full doses must be started at once. If fuller, and perhaps more expert, investigations reveal later a normal blood count, no harm will have been done and thiouracil can be restarted. If, however, they confirm the diagnosis a dangerous delay will have been avoided and recovery is probable; but thereafter thiouracil must not be used on that patient.

Lastly, after the cessation of thiouracil treatment it will be found that about one-third of the patients, although well when taking thiouracil, sooner or later relapse after its omission. The decision how to deal with such cases depends largely on the patients. If they are content to undergo another course of treatment with the drug there is no reason why they should not, and it will be found that the condition rapidly comes under control again on administering their particular maintenance dose. If, however, they are averse from further regular attendances and skilled surgery is available, then, until we have more certain information regarding the results of long-term thiouracil therapy, surgical intervention should be considered.

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LIVER FUNCTION TESTS IN CASES TREATED WITH THIOURACIL COMPOUNDS

BY

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It has long been realized that liver damage occurs in thyrotoxicosis. Changes comprising fatty degeneration, multi-lobular cirrhosis, and acute yellow atrophy have been noted (Schaffer, 1940). Moschowitz (1946) described a cirrhosis, with fibrosis round the radicles of the hepatic artery, due to the increased velocity of blood flow and increased blood volume in the hepatic artery which disturb the pressure relations between the portal vein and the hepatic artery. Stasis occurs round the radicles of the hepatic artery and the lesion begins as capillary congestion. This condition would seem to be the reverse of the centrilobular congestion that occurs in congestive failure of the right side of the heart.

Thiouracil compounds are said to be broken down in the liver (McCullagh, 1946), and might therefore exert a toxic effect, although György and Goldblatt (1945) found that 0.1% thiouracil fed to rats maintained on a cirrhosis-producing diet failed to produce any liver damage. McClosky *et al.* (1947) fed cats for seven to eight months on a high-protein diet and gave doses of up to 300 mg. of thiouracil per kg. daily; they found no more than moderate fatty degeneration of the liver. Hepatogenous jaundice has been reported as an uncommon complication of thiouracil therapy in six cases (Gargill and Lesses, 1945; Sloan and Shorr, 1944; Kahn and Stock, 1944; Livingston and Livingston, 1947). Five patients recovered completely on withdrawal of the drug; the sixth died of associated agranulocytosis. Laparotomy on one case revealed biliary stasis but no other definite lesion (hepatic biopsy). The liver of the patient who died was swollen, with dark-brown parenchyma and distended lobules. Diabetes mellitus was also present. Sloan and Shorr suggest routine icteric indices during initial treatment.

Present Investigation

Serial liver function tests have been carried out at six-monthly intervals over a period of 12 months on 81 patients who were under treatment with thiouracil compounds for thyrotoxicosis. In selecting the tests an attempt was made to combine ease of performance with a maximum of accurate information regarding early liver damage. Generally speaking, the empirical tests of liver function, while not involving the patient in a complicated preparation, are more useful in indicating whether jaundice is hepatocellular or obstructive than in detecting early stages of liver damage. Tests which aim at the detection of slight degrees of liver damage are more cumbersome and time-consuming for the laboratory staff and patients.

The following tests were chosen, having the practical advantage that they could all be performed on a single specimen of 20 ml. of blood. Their value and limitations will be discussed later.

Normal Values

Serum bilirubin ..	0.3-1 mg. per 100 ml.
Serum alkaline phosphatase ..	5-15 King-Armstrong units
Takata-Ara reaction ..	Negative
Thymol turbidity test ..	1-5 units
Total serum protein ..	7-8 mg. per 100 ml.
Albumin ..	4-5.2 mg. per 100 ml.
Globulin ..	2-2.8 mg. per 100 ml.
Albumin/globulin ratio 2:1	