NOTES ON SOME REMEDIES

IV. THIOURACIL

By R. N. CHAUDHURI, M.B., M.R.C.P. (Edin.),
T.D.D. (Wales), F.S.M.F.
Professor of Tropical Medicine, School of Tropical Medicine, Calcutta

The discovery of the action of thiouracil in thyrotoxicosis is the result of alert observation and quick recognition of the significance of certain observed facts. Mackenzie et al. (1941) were studying the effect of sulphaguanidine as an intestinal disinfectant and came to investigate its toxicity to the rat. They noted that animals dying after sulphaguanidine showed goitres which on microscopical section were found to be due to hyperplasia and were practically free from colloid. The same effect was produced more or less by other sulpha drugs such as sulphadiazine and sulphapyridine, and Richter and Clisby (1942) showed that other sulphur compounds, notably thiouracil and its derivative, thiourea, had a well-marked goitrogenic effect. Kennedy (1942) and his colleagues who were investigating the action of rape seed in rat thyroid found the causative agent in allyl-thiourea. These discoveries led to a study of the mode of action of these two compounds, and the investigations that followed revealed that they inhibit the physiological activity of the thyroid gland and produce the somewhat odd combination of hypothyroidism and thyroid hyperplasia. This is interpreted as meaning that the thyroid gland is not producing sufficient hormone, thyroxine, for the needs of the body and is being stimulated to hyperplasia to remedy this deficiency. The cause of the hypothyroidism was at first obscure, it could not be due to any neutralizing action of thiouracil on the hormone for it is abolished by the coincident administration of thyroxine. It was eventually thought, and this was supported by experimental evidence, that the action of thiourea is to prevent the synthesis of the thyroid hormone and that the lack of this hormone is the cause of hypothyroidism. In response to this condition the pituitary gland is stimulated to increase its thyrotropic activity and in turn the thyroid gland becomes hyperplastic, but is unable to relieve the hypothyroid condition owing to blocking of the thyroxine elaborating mechanism. It was Astwood (1943) who suggested and introduced with beneficial results the clinical use of thiourea and thiouracil in hyperthyroidism, a toxicemic state caused by excessive secretion of thyroxine, and since then many confirmatory reports have been published in England and America.

Method and Results of Treatment

Thiouracil, being much less toxic, has now replaced thiourea, though the action of the two preparations is similar. Of late, another derivative, 4-methyl thiouracil, is being used, it is more easily manufactured and is said to be less toxic and give more rapid control of the signs and symptoms. The aim of treatment is to decrease the synthesis of thyroxine to a normal level but not below it, so that the pituitary will not be stimulated to produce the indirect effect of thyroid hyperplasia. The original dose (1 gm.) has now been reduced, for with it toxic effects were frequent. For initial treatment the dose of either drug is usually 200 mg. given by mouth three times a day. Since thiouracil is rapidly absorbed and excreted, the present tendency is to spread the single doses over the day, e.g. to give 6 doses each of 100 mg. in 24 hours. There is a latent period of one to two weeks before the drug comes to action; this is because it has no power to neutralize the thyroxine already formed in the body. This latent period is prolonged by some weeks in patients previously treated with iodine, although iodine given after thiouracil has no such delaying effect. Leys (1945) found the latent period also longer in the chronic cases, but chronicity did not prevent subsequent rapid progress. According to Himsworth (1944) the first change noted is the disappearance of the skin flush, while the last is a fall in pulse rate. The patient feels a sense of well-being, the tremor and palpitation subside, the weight increases, the basal metabolic rate falls and the blood cholesterol rises. The maximum effect is gradually attained in about four weeks. The effect on eye signs is however
not so striking; stare and lid retraction may diminish, but exophthalmos is not appreciably affected, although Wilson (1946) found it considerably reduced in a few patients with recent history. In most cases there is no noticeable reduction in the size of the thyroid gland, indeed it actually increases in size in some cases. As long as the drug is continued, the improvement persists but on its omission the signs of thyrotoxicosis return and disappear again with the resumption of treatment. It is therefore necessary to give a maintenance dose, the principle being to give the smallest dose that would prevent remissions. So when a satisfactory gain in body weight has been attained, i.e. in 3 to 4 weeks time, the dose is reduced to 50 to 100 mg. a day though occasionally a little higher dose may be necessary. Here also it is better to give suitably divided doses per day than only one. Most patients can go back to work in 3 months. Some have remained well up to one year without the drug, but the present evidence is strongly in favour of continuing the administration of thiouracil in small maintenance doses without interruption.

Cases of primary hyperthyroidism, toxic adenoma and recurrent thyrotoxicosis after thyroidectomy all respond to the drug though in varying degree. There is no uniformity in the rate of improvement and the time required for response varies considerably from case to case. Some clinicians have obtained more striking results in definitely toxic goitre than in milder cases, but it should be remembered that the symptoms of tachycardia, tremor, loss of weight and nervousness may be due to other factors than goitre, neurosis in particular, and Cookson (1945) even goes so far as to suggest that if thiouracil has no effect they are probably not due to the goitre. A small proportion of cases prove resistant to treatment but, as Dunlop and Hill (Dunlop et al., 1946) point out, a patient should certainly not be labelled drug resistant simply on account of the persistence of tachycardia and high pulse pressure during the first few weeks of treatment; it may take a long time before these features of thyrotoxicosis are abolished by thiouracil. Still the possibility of some drug resistance should be remembered when patients resume treatment after discontinuance of the drug.

Thiouracil has no effect on anxiety neurosis sometimes associated with thyrotoxicosis. On the other hand it has been found effective in controlling thyrotoxic auricular fibrillation especially when it is of recent origin, but the normal rhythm is not always restored. Cases are on record showing its good effect in early left ventricular failure. Diabetes is no contra-indication to its use.

**Toxic Effects**

Regarded at first as relatively innocuous, thiouracil has during these three years of its discovery grown a long list of toxic reactions but with experience the list tends to become shorter. Toxic manifestations may be due to overdosage or to idiosyncrasy. Gross overdosage causes early enlargement of the goitre which may produce pressure symptoms. Toxic symptoms from chronic slight overdosage are insidious and appear later, and are recognized by coldness, fatigue, depression and a bloated, appearance. But owing to the reduction of the dosage these effects are seldom seen nowadays. Those that are seen at present are more often due to idiosyncrasy and appear in the second week or later during the period of initial treatment and occasionally during the maintenance period. They usually disappear when the drug is withdrawn. The commonest manifestations are skin rashes of various types, adenitis, joint pains, headaches, oedema of feet and gastrointestinal symptoms including nausea, vomiting, abdominal pain and diarrhea. A febrile reaction develops about the end of the first week with or without enlarged spleen. Jaundice has been reported a few times and occasionally there has been complete loss of taste. But its most important effect is on the blood. Thiouracil does not usually depress the white blood cell count as is thought by some, and in assessing its effect it should be noted that slight leucopenia is usual in untreated toxic goitre. Nevertheless, the drug may lead to definite leucopenia and neutropenia in some cases. Neutropenia can develop into agranulocytosis if the drug is continued but usually returns to normal if it is omitted or given in reduced dosage for a few days. Two surveys made in the U.S.A. by Moore (1946) and by Van Winkle et al. (1946) respectively covering 1,091 and 5,745 patients treated with thiouracil showed that agranulocytosis occurred in a little more than 2 per cent of cases, and caused death in 0.4 per cent; more than 70 per cent of cases of agranulocytosis developed within the first eight weeks of treatment. No relation could be discovered between the incidence and dosage. Other toxic effects were found in about 10 per cent, the commonest being fever, glandular enlargement and various types of rash. Reports on more recent series of cases are encouraging and indicate fewer toxic signs and symptoms. However, agranulocytosis is still a definite risk, and the drug should not be used where there are no facilities for frequent white cell counts and if the white blood count falls below 3,000 the drug should be stopped. And it is also important to instruct the patient to report development of any fresh symptoms, a sore throat in particular, for agranulocytosis often comes on suddenly without warning. For prevention various remedies have been suggested besides keeping to a minimum effective dose: folic acid, protelysed liver, various members of the vitamin B complex and intravenous injection of pyridoxine hydrochloride.

Pregnancy is no contra-indication to the use of thiouracil so far as the mother is concerned,
but Goldsmith et al. (1945) found that its administration to pregnant rats resulted in activation and hyperplasia of the thyroid gland and retarded growth of the offspring. These effects were however transient and disappeared when the young rats ceased to imbibe the milk of thiouracil-treated mothers. Eaton (1945) reports the case of a woman who was on this drug during pregnancy. The child after birth had an enlarged thyroid gland but was normal in all other respects. At the age of three months the gland was no longer apparent and growth had been normal. Davis and Forbes (1945) found post-mortem enlargement and hyperplasia of the gland in a fetus six months old, the mother having been on thiouracil for nearly a year. These findings are of practical importance. Though the effects appear to be transient, the administration of thiouracil to pregnant women calls for caution and Eaton suggests that it should be replaced by iodine some weeks before delivery.

Advantages and Disadvantages

The cause of exophthalmic goitre is still unknown and treatment has hitherto been directed towards reducing the circulating thyroxine, whether it be by surgery, by x-rays or by drugs such as iodine and thiouracil. It is too early to say what the ultimate effect of thiouracil may be. According to Marine's researches (1935) long-continued hyperplasia of the thyroid eventually gives way to atrophy of the gland, and if we can tide the patient over with thiouracil until this occurs, the state of thyrotoxicosis may be cured. There seems no reason to suppose that its careful use will result in such atrophy as will cause undesirable hypothyroidism. On the other hand, it may be that the disease involves a vicious circle of stimulation of the thyroid by the pituitary and stimulation of the pituitary by the thyroxine and that thiouracil, by breaking the circle helps the thyroid to return to a relatively normal state and a cure is thereby obtained. Meanwhile, whatever be the mechanism and the end result, its use must be discriminating and the following observations may be of help to practitioners in applying it clinically.

Thiouracil has proved very effective in the treatment of thyrotoxicosis, though under certain conditions it may fail. It has two drawbacks: one is its toxicity, but there are grounds for believing that with increasing experience these effects will be further reduced or become insignificant. Its potential dangers need not deter any one using it so long as he observes the precautions already indicated. The second drawback is the necessity for continuing the maintenance dose for an indefinite period, and this is troublesome to both the patient and his medical attendant. Surgery, on the other hand, is the quickest way to ensure recovery from thyrotoxicosis. The operation of thyroidectomy has attained a high degree of perfection in expert hands. Patients suffering from pressure symptoms will require surgical treatment on account of the tendency of the drug in some cases to cause enlargement of the gland. Surgery should also be the choice for patients with a retro-sternal goitre or with pronounced enlargement of the gland, and for those few who are drug resistant or show persistent reactions to it. Apart from these considerations, thiouracil may be tried first in most cases. It is more potent and more permanent in action than iodine, but as its effects are not immediately seen, iodine should be required when rapid action is required as in thyroid crisis. In the elderly with cardiovascular complications and in children thiouracil has advantages over operation. It is the obvious choice for those who are averse to operation. There are some patients unsuitable for thyroidectomy or who relapse after such treatment; they usually respond well to thiouracil. It is also very important in preoperative treatment as it can be relied upon to detoxicate the patient and obviate the post-thyroidectomy crisis due to the liberation at operation of hormone stored in the gland. On the other hand, it causes the gland more vascular, causing troublesome bleeding during operation, this can be avoided by reverting to iodine a few days before the operation.

To summarize we have in thiouracil a weapon almost as effective as surgical treatment in selected cases. There are risks, and these should be realized so that treatment should not be haphazard and uncontrolled.

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