

evidence of enlargement of some of the coils of the small gut, probably involving only the ileum. The appearances are consistent with partial obstruction such as could be produced by adhesions. No definite filling defect was seen in the lumen of the small gut."

Operation (anaesthetist, Dr. O. Carden Sibley; gas, oxygen, ether).—At laparotomy the small intestine was seen to be moderately distended but no obstruction was found. Hard glands were palpable in the upper part of the mesentery of the small intestine and a growth was found in the body of the pancreas, spanning the aorta, fixed to the posterior abdominal wall and quite irremovable. The large intestine was of normal size. A gland was taken for section and the abdomen was closed.

The patient became progressively distended after the operation despite gastric suction and intravenous glucose and saline, partly burst his wound, and died on the fourth post-operative day. No necropsy was obtained, but the gland removed at operation showed replacement by masses of undifferentiated carcinoma.

Discussion

A somewhat cursory search of the literature shortly after the patient had died, and discussion with colleagues, failed to throw any light on the matter. Ogilvie, who likewise failed to find any reference to the subject in the literature, appears to be the first to publish a description of this unusual syndrome. The manner of its production is of great but academic interest, since the symptoms are produced only after inextricable invasion by carcinoma of a relatively inaccessible region of the body. Ogilvie considers three methods by which the symptoms might be produced: (1) by parasympathetic stimulation from invasion by the tumour; (2) by secretion of a cholinergic substance by the tumour cells; or (3) by sympathetic paresis from invasion by the tumour. He believes, despite some contrary points, that the last is the probable explanation.

A fourth explanation might be considered in my case—that interference with the blood supply by pressure of the tumour on the superior mesenteric vessels might have evoked the symptoms. Mesenteric thrombosis will cause colic, borborygmi, and distension, though the picture is more acute. Against this theory is the fact that my patient's intestine showed no cyanosis. In Ogilvie's first case there was evidence that the pelvic colon was greatly affected, though the tumour cannot have caused interference with the inferior mesenteric artery. It seems, therefore, that the vascular hypothesis must fall down.

A carefully detailed post-mortem examination of a similar case might clear up the mystery, and it is to be hoped that it will be forthcoming.

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THIOURACIL IN THYROTOXICOSIS

BY

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In this department 62 patients with thyrotoxicosis have been under treatment with thiouracil or methyl thiouracil for periods between 6 months and 4½ years. The series includes all cases of thyrotoxicosis admitted to the ward except a few so mild that phenobarbitone alone was used in treatment. The general results of treatment are here briefly recorded, and certain aspects of management in relation to auricular fibrillation, pregnancy, and granulopenia are discussed in the light of the experience gained.

Particulars of a Series of Cases

The distribution of cases by age, sex, and the presence or absence of exophthalmos is shown in Table I. Ten of the patients were males and 52 were females; their ages varied from 16 to 66 years. Exophthalmos was more common among the younger patients. No attempt was made to differentiate between primary and secondary thyrotoxicosis, and in only one case was there a definite history of an enlargement of the thyroid preceding the thyrotoxicosis by several years.

TABLE I

Age:	10-19		20-29		30-39		40-49		50-59		60-69							
	M	F	M	F	M	F	M	F	M	F	M	F						
Eyes	E	O	E	O	E	O	E	O	E	O	E	O						
No.	1	2	1	2	6	1	2	8	3	1	2	10	6	1	4	3	1	7

E = Exophthalmos present. O = No exophthalmos present.

All cases were admitted to the ward for treatment, and the effect of rest in bed and 1 gr. (65 mg.) of phenobarbitone three times a day was observed for one to three weeks. When the sleeping pulse had settled to a constant level for several nights, and the patient's symptoms showed no tendency to abate further on this treatment, the basal metabolic rate was estimated with the Benedict-Roth apparatus on two successive mornings, and treatment with thiouracil or methyl thiouracil was begun. The dose of thiouracil used at first was 0.6 g. daily, and this proved effective in all cases. Later 0.2 g. was tried, but, while this would control thyrotoxicosis of mild or moderate degree, it failed to do so in two severe cases. It was found, however, that 0.4 g. of thiouracil daily was as effective an initial dose as 0.6 g. Methyl thiouracil proved equally satisfactory in doses of 0.2 g. daily, and is now used for all cases. Each patient's progress was followed clinically and assessed every ten days, when the basal metabolic rate was estimated. After three weeks on thiouracil the patient was usually discharged on a maintenance dose of 0.2 g. of thiouracil or 0.1 g. of methyl thiouracil daily, and was seen thereafter at intervals of six weeks. White cell counts were done twice a week in hospital, and at each out-patient attendance, although it was realized that they were of no value as indicators of impending agranulocytosis. They served to remind the patients of the possible dangers of the treatment, which had been explained to them in the ward, and revealed several cases of granulopenia.

Most cases were adequately controlled by 0.1 g. of methyl thiouracil daily or less; some required 0.15 g. The dose was decided on a clinical estimate of the patients' condition when they reported to the follow-up clinic. No single observation was found to be completely trustworthy, but a reasonably accurate idea of the state of the patients was obtained by asking them how they felt, how much

A six-months training course for hospital records officers is being jointly run until about the end of July by the Association of Medical Records Officers, the King Edward's Hospital Fund for London, and the Board of Governors of the Middlesex Hospital. It is hoped that similar courses will be organized later. The Ministry of Health states that the Minister welcomes the growing interest of hospitals in the proper maintenance and organization of patients' records and the decision of many of them to overhaul their records systems and appoint designated records officers. If this development is not to go astray only adequately trained or experienced officers should be appointed; and boards and committees thinking of making such appointments should defer doing so, unless there are exceptional reasons for immediate action, until there are enough really suitable candidates. Some boards and committees may be considering buying more or less elaborate equipment, such as punched card machinery, for their records departments. The Minister appreciates the value of such equipment where the volume of work makes it an economic proposition, but he is advised that the circumstances of a single hospital, or even in many instances of a management committee group, do not normally justify its purchase. No steps of this kind should therefore be taken by management committees without consultation with the regional hospital board.

work they could comfortably do, and whether they got any palpitations; also by noting the weight, resting pulse rate, state of the skin, and presence or absence of tremor. The size of the thyroid gland was also noted.

Thiouracil effectively controlled the thyrotoxicosis in all cases, and the majority were back in full employment within six weeks of starting treatment. All patients were told that they should regard themselves as restored completely to normal as a result of the treatment, and only two of the 59 cases given thiouracil alone have not returned to full activity. One is a woman with advanced spondylitis ankylopoietica who cannot do heavy housework, and the other a country postman who could not continue his bicycle deliveries. He is now working as a taxi driver. Most of the patients are housewives, and all except a few over 60 do their own housework, including scrubbing and polishing floors. Four are crofters' wives and had returned to full activity within six weeks of starting thiouracil, as had two men in very heavy employment—one a cyclist messenger, and one who does a full day's work shovelling granite into a crusher. A railway-track layer was doing light work in four weeks and full work in eight weeks after starting thiouracil. The two patients still at school also lead normal lives without any restrictions.

TABLE II.—*The Position in 1948*

Duration of Treatment (Months)	Group 1	Group 2	Group 3	Group 4	Total
6-12 ..	2	7	0	0	9
12-18 ..	9	3	0	0	12
18-24 ..	5	3	1	0	9
24-30 ..	4	7	0	0	11
30-36 ..	2	1	0	0	3
36-42 ..	4	2	0	0	6
42-48 ..	3	0	0	0	3
48-54 ..	2	0	1	1	4
54-60 ..	2	0	0	0	2
Totals ..	33	23	2	1	59

Group 1: Off thiouracil for three months or more and satisfactory.

Group 2: On thiouracil and satisfactory.

Group 3: On thiouracil and unsatisfactory.

Group 4: Off thiouracil and unsatisfactory.

The position of the cases in the series in June, 1948, is shown in Table II. Of 13 patients who have been under observation for three years or more, five have taken no thiouracil for 33 to 39 months and have not relapsed; three have taken none for 21 to 31 months; three relapsed off thiouracil, two of them again being controlled by thiouracil; and two have been taken off thiouracil within the last six months. Three patients are classified as unsatisfactory: (1) The patient off thiouracil is the only one in the series who developed a granulopenia with infection. She refused operation, and, although living a normal life looking after her family, is moderately thyrotoxic. (2) This patient is adequately controlled by thiouracil, but has many symptoms caused by her life being spent in three rooms with her husband, two children, and her mother-in-law. (3) This patient feels well and does all her own housework, but has a persistent tachycardia and appears to be slightly toxic. She states that visiting the hospital always makes her nervous.

Three cases are not included in Table II, and are accounted for as follows. One man aged 23 died of suppurative bronchiectasis. His thyrotoxicosis was under control at the time of death. Thyroidectomy has been performed on the other two patients. One of these was a man aged 30 who had previously been treated by deep x-ray therapy for polycythaemia rubra vera and developed a persistent granulopenia on thiouracil. Before thyroidectomy, when taking thiouracil, he was fit and doing full outdoor work as a gas-meter inspector. Now, fifteen months after thyroidectomy, he feels fit, but can only do

clerical work indoors, and is easily made breathless by exertion. In addition, the fine tremor of the fingers has returned, the skin is silken and sweaty, and there is a slight increase in the pulse rate, which, however, was never reduced below 90 per minute by thiouracil. The basal metabolic rate is 95% of normal. In the other case thyroidectomy was performed because of the great increase in the size of the thyroid.

Size of Thyroid

The size of the thyroid was estimated at each visit by inspection and palpation. Four categories were made: slight enlargement, when there was no visible goitre; slight to moderate enlargement, when the enlargement was noticeable only when the patient swallowed; moderate enlargement, when an obvious goitre was present; and large. In most cases there was some increase in the size of the thyroid after treatment began, but usually this was only slight and regression occurred after six months to a year.

At present two patients have large goitres which cause no inconvenience. No thyroidectomy has been advised, as in both cases some decrease in size is expected. Two other patients had large goitres, but one of these has been removed surgically and the other has regressed to slight to moderate size, thiouracil administration having ceased. One patient with a moderate enlargement underwent thyroidectomy, and five patients at one time showed moderate enlargement, but in all these cases the thyroid is now small. Four patients have thyroids of slight to moderate size, and in eight the thyroid has shrunk from this size to only slight enlargement. In the remaining 40 cases the enlargement is slight.

Complications due to Thiouracil

In five cases skin rashes have occurred in the early weeks of thiouracil therapy. Unfortunately, as all the patients were at the time taking phenobarbitone it is impossible to be sure whether this drug or the thiouracil was responsible. In all cases the rashes faded in a few days after withholding phenobarbitone.

An unexplained fever occurred in four cases, but the temperature settled to normal in a few days without any alteration in treatment.

Granulopenia (less than 1,000 neutrophil polymorphs per c.mm. of blood) has been noted in eight cases. One patient reported because she had developed a sore throat. She had originally presented with thyrotoxicosis in July, 1944, and had been treated with thiouracil for 16 months, thiouracil then being stopped. She had remained in good health without thiouracil for 18 months, when a mild relapse occurred. Thiouracil, 0.2 g. daily, was given once more. On the sixth day after beginning thiouracil her granulocyte count was 2,100 per c.mm.; three days later a sore throat developed, and the next day she was found to have 186 granulocytes per c.mm. of blood. Thiouracil therapy was stopped and penicillin was given. The cell count rose rapidly, and on the third day after stopping thiouracil showed 2,600 granulocytes.

In the remaining seven cases of granulopenia there were no symptoms or signs of any infective process, the granulopenia being revealed by routine blood examination. The duration of treatment before the onset of granulopenia in these cases varied from four weeks to 16 months. In three cases the polymorph count was 384, 400, and 440 cells per c.mm., but the patients felt in their usual state of health. In all seven cases the cell count rose rapidly when thiouracil was stopped, and none developed an infection or was given any antibiotic treatment.

The further management of patients who have had granulopenia has varied. As already mentioned, the one who developed an infection refused operation and is moderately toxic, and one with granulopenia and no infection has had a thyroidectomy. Four patients have resumed treatment with thiouracil or methyl thiouracil, and over periods varying from six to 18 months have shown no further granulopenia. One patient proved sensitive to both thiouracil and methyl thiouracil, but after a slight relapse off thiouracil his condition is satisfactory. In the last case the granulopenia occurred on the day that thiouracil was stopped for a period of observation, and so far no thyrotoxic symptoms have recurred. In cases given thiouracil after having had a granulopenia the white cell count has been observed three times weekly for the first month and thereafter every six weeks.

Other Complications

Myxoedema occurred in a woman aged 66 who was admitted with severe thyrotoxicosis complicated by an acute mania. She responded rapidly to thiouracil, and medication was stopped after seven months. Nineteen months after cessation of the thiouracil she was found to be severely myxoedematous, with a basal metabolic rate 71% of normal. The myxoedema in this case is not likely to be the result of thiouracil administration.

Diplopia occurred in two cases. In one it lasted for only a few weeks during the early months of treatment. In the other it was a troublesome symptom that persisted for about six months. The cause was probably exophthalmic ophthalmoplegia.

Pregnancy

There have been three pregnancies in women taking thiouracil. In the first case the mother was kept on thiouracil throughout pregnancy. The infant was born alive with an easily palpable, rather hard thyroid. This became impalpable after feeding for one month on pooled human milk, and the infant is now a normal child of 2½ years. In the second pregnancy thiouracil was not given for two months before delivery; Lugol's iodine, 10 minims (0.6 ml.) daily, was given instead. A normal infant was born. In the third pregnancy thiouracil was stopped four months before delivery and iodine was not given. A normal infant was born in this case also. Both pregnancies in which the thiouracil was stopped before delivery were followed by relapse of the thyrotoxicosis within three months of delivery.

Auricular Fibrillation

Ten cases of thyrotoxicosis complicated by auricular fibrillation have been treated. In four the fibrillation was continuous and was associated with congestive heart failure, but in all cases the history suggested that failure had been present for only a few weeks. In the first case regular rhythm was established after 15 days' treatment with thiouracil alone. In the second, auricular fibrillation persisted after nine weeks' treatment with thiouracil alone, although the thyrotoxicosis appeared to have been controlled. When regular rhythm was restored by quinidine after digitalization a transient motor aphasia occurred, presumably the result of a cerebral embolism. The third and fourth cases were treated successfully by quinidine on admission to restore regular rhythm, and then by thiouracil to control the thyrotoxicosis. In five patients paroxysmal fibrillation was shown by electrocardiography to be present. In four of these the fibrillation was controlled by thiouracil alone, but in the fifth the paroxysms of fibrillation were so frequent and the patient's condition so distressed by cardiac failure that digitalis was given, and regular rhythm

was restored by quinidine before thiouracil was used. In the tenth case fibrillation was known to have been present for three years and heart failure for two months. The patient had been receiving digitalis since the onset of the fibrillation. She was treated by complete rest in bed and injections of mersalyl, and methyl thiouracil, 0.2 g. daily, with steady improvement. After three weeks the digitalis was stopped and the improvement continued. The oedema had gone after six weeks.

In all ten cases, once the thyrotoxicosis was adequately controlled, the administration of digitalis and quinidine, if they had been given, was stopped, and treatment was continued with thiouracil alone. In the last case slow fibrillation continues without evidence of heart failure, but in the others no recurrence of fibrillation has been observed while on thiouracil. The periods of observation since restoration of regular rhythm vary from seven to 27 months.

Koilonychia

Koilonychia has been noted in seven of the 51 cases seen between October, 1945, and January, 1948 (Table III). All

TABLE III.—Showing the Haemoglobin Level in the Patients having Koilonychia

Case	Haemoglobin on Admission	Haemoglobin After 1 Year
1	86%	86%
2	85%	86%
3	68%	68%
4	78%	94%
5	94%	—
6	45%	—
7	86%	—

were in women, and a history of thyrotoxicosis lasting a year or more before reporting for treatment was usual. Only Case 6 was given iron. The haemoglobin level (Haldane) on admission is shown in the table. In four of the cases in which one year's follow-up has been possible the koilonychia has entirely disappeared and a normal strong nail has grown. None of these cases was given iron, and in three there was no rise in the haemoglobin level.

Discussion

In this series of cases thiouracil has proved satisfactory in the treatment of thyrotoxicosis, and only one patient of those given thiouracil alone has had to obtain lighter employment because of the disease. The disability in this case was probably less than that of the first patient who had a thyroidectomy and in whom symptoms returned after the operation despite a basal metabolic rate 95% of normal. The symptoms in this latter case are similar to those described by Martin (1948), and it is curious that they were not present when the basal metabolic rate was reduced to 100% by thiouracil.

The one serious complication encountered has been granulopenia, and only a high degree of co-operation on the part of the patients has avoided a catastrophe. Several have reported to the hospital or to their own doctors with sore throats, but only one was found to have a granulopenia. The position of those in whom a granulopenia was discovered by routine blood examination is not certain. Agranulocytosis usually occurs with great rapidity, as in the case in the present series, and in the only patient with granulopenia whom it was possible to keep in hospital for observation the neutrophil polymorph count remained low for 18 days while thiouracil was given, rose when thiouracil was withheld, and remained normal when methyl thiouracil was used. This suggests that granulopenia is not necessarily a prelude to agranulocytosis. Five patients who developed granulopenia were again given thiouracil or methyl thiouracil after an interval off the drug had allowed

recovery. Only one of these developed a further granulopenia, which appeared in the first few days after starting the drug.

The management in pregnancy is a matter requiring further observation. The enlargement of the infant thyroid that was found when thiouracil was given throughout pregnancy has been previously reported by Eaton (1945). It is probably best to stop thiouracil administration some months before delivery. As thiouracil is excreted in maternal milk no mother taking thiouracil should suckle her child (Williams *et al.*, 1944; Chesley, 1944).

Although thiouracil alone may restore regular rhythm in thyrotoxic auricular fibrillation it does not always do so, and sometimes, when the thyrotoxicosis is slow in responding, may take a long time, during which there is some danger of embolism. After the episode of embolism which occurred in the second case with auricular fibrillation it was thought safest to establish regular rhythm with quinidine at the earliest possible moment in all cases where the fibrillation was not of long duration. Accordingly such cases were admitted as emergencies to the ward, digitalized on admission, and then given quinidine. In many cases, however, like the one here reported, the fibrillation may be allowed to continue and the heart failure will respond to thiouracil alone (Cookson and Staines, 1947).

Koilonychia has been noted previously in thyrotoxicosis and its disappearance after treatment with thiouracil reported by Cooke and Luty (1944). It is evident from their records, and from the observations on the first three cases shown in Table III, that the koilonychia in thyrotoxicosis is unrelated to the haemoglobin level.

Summary

A series of 62 consecutive cases of thyrotoxicosis were treated with thiouracil or methyl thiouracil. All cases responded to the drug, and only one man treated with thiouracil alone had to obtain lighter employment. The time spent off work was usually less than six weeks from starting thiouracil therapy. In three cases the results were regarded as unsatisfactory.

Thyroidectomy was performed in two cases, the indications being persistent granulopenia and excessive thyroid enlargement respectively. One patient died from suppurative bronchiectasis.

Granulopenia occurred in eight cases. In one there was infection, which was controlled by penicillin; the others were found on routine blood examination. Four of these cases have resumed thiouracil therapy without further granulopenia.

One patient developed myxoedema after being off thiouracil for 19 months.

Two patients developed transient diplopia, probably due to exophthalmic ophthalmoplegia.

Three pregnancies occurred. Thyroid enlargement was noted in the child in the only case in which thiouracil was given throughout pregnancy.

The treatment adopted for continuous auricular fibrillation of short duration was to restore regular rhythm with quinidine as soon as possible, and to stop quinidine administration when the thyrotoxicosis was controlled. Paroxysmal fibrillation responded to thiouracil alone.

Koilonychia was noted in seven of 51 cases. In three of these normal nails were formed in about one year without any rise in haemoglobin.

I wish to thank Professor R. S. Aitken for giving me charge of these patients during my term as his assistant.

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THYROTOXIC AURICULAR FIBRILLATION TREATED WITH THIOURACIL

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Thiouracil compounds have been shown to be effective in causing reversion to sinus rhythm in cases of thyrotoxic auricular fibrillation. Cookson (1945) secured reversion in three out of 10 cases treated with thiouracil alone, but noted that one of his failures had mitral stenosis. Out of Nussey's (1944) three patients sinus rhythm was restored by thiouracil in one. In a later paper Cookson and Staines (1947) claimed reversion to sinus rhythm with thiouracil alone in eight out of 16 patients after an average of 35 days' treatment, the longest period being 15 weeks and the shortest four days. Associated cardiac disabilities (mitral stenosis) are reported in only one of the patients with persistent fibrillation, McGavack and others (1945) reported reversion to sinus rhythm with thiouracil alone in 12 out of 18 patients, one of the 12 having bundle-branch block. Grainger's (1945) two patients with fibrillation both reverted spontaneously to sinus rhythm. Clarke (1948) achieved reversion to sinus rhythm in three out of six patients with thiouracil alone, while Wilson (1946) reported reversion to sinus rhythm in five out of six cases included in the present series.

The object of this communication is to present briefly the effect of treatment with thiouracil drugs on cases of auricular fibrillation due to thyrotoxicosis, and to determine the value of certain associated factors in assessing the likelihood of reversion to sinus rhythm without additional therapy. Out of 144 thyrotoxic patients attending the endocrine clinic 28 (19%) had auricular fibrillation. All had been treated with thiouracil compounds (thiouracil, methyl thiouracil, or propyl thiouracil) for not longer than two years, and were cases of secondary thyrotoxicosis. Their ages ranged from 32 to 68 years (average, 50). Thirteen patients reverted to sinus rhythm with thiouracil treatment: quinidine was deliberately omitted in order to investigate the long-term effects of thiouracil on auricular fibrillation. The average amount of thiouracil compound given was 50 mg. daily. Six of the patients received digitalis to control ventricular rate and congestive failure.

Apart from 11 patients who had a systolic blood pressure of 160 mm. Hg or greater, there was no clinical evidence of cardiovascular disease. Cardiomegaly was present in 18 cases. In no case was the systolic blood pressure greater than 190 mm. Hg. Two patients with persistent auricular fibrillation have been excluded from the analysis, as the thyrotoxicosis is not yet under control.

Group I: Patients in whom Auricular Fibrillation Persisted

In each of the 13 patients in this group the thyrotoxicosis was well controlled but the fibrillation persisted. The average age was 52 years, and the duration of symptoms before treatment varied from three months to 12 years, the average being 77 months. The duration of treatment up to the present has varied from one month to two years, the average being 11 months. Before treatment was started five patients had a systolic blood pressure of 160 mm. Hg or greater, while slight to moderate cardiomegaly was present in nine patients. The cases are summarized in Table I.