BRITISH MEDICAL JOURNAL

LONDON SATURDAY DECEMBER 9 1944

TREATMENT OF HYPERTHYROIDISM WITH THIOURACIL

BY

A. M. NUSSEY, M.D., M.R.C.P.

Physician to Selly Oak Hospital, Birmingham

Until recently partial thyroidectomy was the treatment of choice for thyrotoxicosis. X rays and radium had their advocates, and some continued to pin their faith to iodine, either alone or in combination with various sedatives. It is true that in quite a number of mild cases of thyrotoxicosis the disease would abate spontaneously; but only too often, especially in severe instances, the patient treated medically for too long would become a physical, sometimes a mental, wreck, or fall an easy prey to intercurrent infection. The advent of thiourea, and especially of thiouracil, bids fair to alter the position radically. These preparations may represent only a milestone in the approach to a problem the real key to which may be a substance acting through the pituitary; but at present, to say the least, they offer a serious challenge to the hitherto undisputed sway of surgery in the treatment of hyperthyroidism. The use of thiourea and thiouracil in thyrotoxicosis is an example of how seemingly unrelated research may sometimes, almost by accident, be turned to advantage in treatment of disease. This research began when the Mackenzies and McCollum (1941), working on the effects of sulphaguanidine in rats, discovered that it had the property of inducing a hypothyroid state and enlargement of the thyroid gland in the experimental animals. At about the same time similar results were obtained by Richter and Clisby (1941, 1942), who used phenyl thiourea, and by Kennedy (1942), who used allyl thiourea which he isolated from rape seed. Later the Mackenzies (1943), and Astwood and his colleagues (1943), proved that, besides sulphaguanidine, other sulphonamide derivatives, and to a lesser degree sulphanilamide itself, also had the power to depress metabolism and cause hypertrophy of the thyroid gland in rats. In an endeavour to find a metabolic depressant suitable for clinical use these workers then tested a large number of compounds, and found that thiourea and thiouracil were the most effective and least toxic. These observations led to the first clinical trial by Astwood (1943).

The original workers and those who followed are all agreed that thiourea and thiouracil probably act by preventing the union of tyrosine and iodine into di-iodotyrosine, which is a precursor of thyroxine. Once thyroxine is present in the body thiourea and its derivatives cannot stop its action. This explains the lag observed in clinical response of thyrotoxicosis to thiourea and thiouracil, and is in keeping with the observation that desiccated thyroid gland is capable of counteracting the effects of these substances in experimental animals. Further light on the mode of action of thiourea is thrown by the paper of Campbell, Landgrebe, and Morgan (1944), who pointed out the great affinity of thiourea for iodine and have shown that thiourea given by mouth is quickly absorbed from the intestine, widely diffused through the tissue fluids, and very rapidly excreted unchanged in the urine. Williams and Bissell (1943), who successfully treated 9 cases of thyrotoxicosis with thiouracil, noted equally rapid absorption and excretion of this substance. They stated that blood analyses of 4 of their cases showed in each a fall of the protein-bound iodine to a normal or subnormal level. More recently Williams and his

associates (1944a, 1944b) devised a method for the estimation of thiouracil in the blood, tissues, and urine, but whether such biochemical tests will prove a help in regulating the dose of the drug remains to be seen.

At present it is possible, when treating patients, inadvertently to exceed the optimum dose and to cause an increase in the size of the thyroid gland and a condition resembling myxoedema. The reason for these complications is presumably the same as that put forward by the experimental workers—namely, that when the supply of thyroxine falls below the needs of the body the pituitary gland is stimulated to excessive secretion of the thyrotrophic hormone, which in turn causes hyperplasia of the thyroid gland. This must have happened to the first patient described by Astwood (1943), to another given in detail by Himsworth (1943) in his first series of 6 cases treated with thiourea, and to several patients in the present series. Other complications known at present are granulopenia, thrombocytopenia, enlargement of lymph glands and spleen, fever, and skin eruptions, but these have been more frequently noted when thiourea was used (Newcomb and Deane, 1944; St. Johnston, 1944; and Astwood's first case, 1943). Now that the more palatable and less toxic thiouracil is freely available there is no reason why thiourea should be employed any longer. It is true that, using thiouracil, Gabrilove and Kert (1943) found that out of 9 cases they treated for thyrotoxicosis one developed fever, generalized enlargement of the lymph glands, and dermatitis, another fever and dermatitis, and a third moderate leucopenia, but their patients were all given rather heavy doses of the drug in addition to an unspecified quantity of barbiturates.

In a discussion on thiouracil at the Royal Society of Medicine, Himsworth (Himsworth *et al.*, 1944) drew a distinction between idiosyncrasy to the drug, which is liable to occur early, and toxic effects which follow prolonged overdosage. Under manifestations of idiosyncrasy he listed the complications mentioned above, and the toxic effects of overdosage he described as superficially resembling myxoedema. Of those taking part in the discussion Drs. H. P. Himsworth, E. P. Sharpey-Schafer, and H. Evans were favourably impressed with thiouracil. One of Himsworth's patients, who had rather large doses, died of agranulocytosis, and two of his other patients, whose goitres increased unduly as a result of the treatment, had to be operated on. Mr. C. Joll (Himsworth *et al.*, 1944), who used thiourea and thiouracil in 20 to 30 cases, presented results in 9, in which, in his opinion, the length of treatment justified making deductions. His failure to achieve success in 3 out of the 9 subjects was criticized at the discussion by Himsworth on the ground that in these iodine was used before thiouracil, and that the latter was not given a sufficiently long trial. Himsworth stated that he found no difference in response to thiouracil in either primary or secondary thyrotoxicosis. The cases mentioned in the discussion at the R.S.M. bring up the number of those fully reported to over 100.

It is obvious that further and more prolonged observations will be required before the treatment of thyrotoxicosis with

thiouracil can be placed on a more satisfactory basis. As a contribution to the problem a presentation is made of the data obtained from personal observations on 27 patients treated at Selly Oak Hospital for periods varying from a year down to 3 weeks. The results are summarized briefly in the accompanying table.

Discussion

The cases are classified into very severe, severe, moderate, and mild, partly on clinical grounds and partly on the basis of a routine preliminary B.M.R. estimation. The majority of

patients had general enlargement of the thyroid gland, others had a nodular goitre, and both types responded to thiouracil equally well—a point already noted by Himsworth. In every instance except in Nos. 8 and 12 the initial treatment was administered while in hospital, thus making possible day-to-day observation of progress. Periods varying from 2 to 11 weeks passed before satisfactory clinical response was noted. The average stay in hospital was about 3 weeks. During that time no other drug, not even a simple sedative, was allowed. Where iodine was found to have been given, it was discontinued

TABLE OF RESULTS

A	B	C	D	E	F	G	H	I	J	K
1	35 F	18 mths.	Moderate	+29%	23/10/43	23/11/43: +15 11/5/44: +2 25/8/44: +11	—	23/11/43: 6,200, 71% 11/12/43: 7,600, 61% 8/1/44: 5,800, 69% 26/2/44: 5,200, 66% 1/11/44: 5,800, 71%	23 lb.	Initial treatment with thiourea tolerated badly. Transient rash when changed to thiouracil. At one time considerable swelling of neck, which disappeared on reducing the dose. Possible to omit treatment for 4 mths., but it had to be resumed a month ago
2	54 F	6 "	"	+27%	23/10/43	4/11/43: +19 17/11/43: +5 3/2/44: +21 9/8/44: +10	—	26/11/43: 6,055, 55% 19/1/44: 7,200, 41% 1/2/44: 7,800, 51% 2/5/44: 6,200, 58% 1/11/44: 5,600, 74% 19/11/43: 9,600, 71% 4/10/44: 9,200, 70%	10 lb.	Given 53 g. of thiourea before change to thiouracil on 11/11/43. Tolerated both well. Now on 0.05 g. of thiouracil daily
3	40 F	12 "	"	+31%	25/10/43	8/11/43: +16 20/11/43: +12 3/5/44: +10	—	30/11/43: 5,000, 45% 10/1/44: 4,400, 62% 3/5/44: 4,200, 47% 8/7/44: 4,200, 47% 2/8/44: 3,600, 55%	Nil	Had 25 g. of thiourea. Changed to thiouracil on 11/11/43. After end of Jan. did not attend till May, 1944, when there was no evidence of relapse. Now recurrence of mild features of thyrotoxicosis and 0.2 g. thiouracil resumed on 4/10/44
4	28 F	15 "	Severe	+45%	22/11/43	7/12/43: +26 12/1/44: +8 19/6/44: +29	—	30/11/43: 5,000, 45% 10/1/44: 4,400, 62% 3/5/44: 4,200, 47% 8/7/44: 4,200, 47% 2/8/44: 3,600, 55%	6 lb.	Some days before treatment with thiouracil admitted with influenzal bronchopneumonia and given sulphathiazole. Has rheumatic mitral disease; her auricular fibrillation reverted to normal during treatment. At one time excessive increase in weight and enlargement of neck noted. This subsided when dose of thiouracil was reduced. Now on 0.05 g. daily
5	53 M	12 "	Very severe	+67%	23/11/43	6/12/43: +41 20/12/43: +18 17/1/44: +20	—	25/11/43: 5,600, 62% 7/12/43: 8,600, 75% 3/2/44: 4,600, 66% 17/3/44: 4,000, 58% 14/6/44: 5,200, 36% 6/9/44: 10,600, 59% 4/10/44: 5,600, 64% 1/11/44: 6,800, 57% 4/12/43: 6,200, 48%	15 lb.	Temporary increase in size of goitre reversed by reduction in dose. Treatment omitted for 2 months, after drug given for 5 months, but had to be resumed; now on 0.1 g. daily. Able to do heavy work
6	65 F	18 yrs.	Severe	+45%	25/11/43	13/12/43: +42	—	14/12/43: 6,300 13/1/44: 8,700, 75% 2/3/44: 7,600, 74% 19/6/44: 5,000, 53% 4/8/44: 7,000, 34% 10/1/44: 7,000, 84% 19/2/44: 10,000, 49% 17/4/44: 10,400, 59%	1 lb.	Partial thyroidectomy 18 years before. In-patient for 1 month. Died early in Jan., 1944, 3 weeks after leaving hospital
7	29 F	1 yr.	Mild	+19%	11/12/43	22/12/43: +9 29/4/44: +25 7/7/44: +11	5,600; 79%	14/12/43: 6,300 13/1/44: 8,700, 75% 2/3/44: 7,600, 74% 19/6/44: 5,000, 53% 4/8/44: 7,000, 34% 10/1/44: 7,000, 84% 19/2/44: 10,000, 49% 17/4/44: 10,400, 59%	Nil	Tachycardia was an outstanding feature; pulse of 100-120 per min. down to 90 after 8 months of treatment. Now on 0.05 g. thiouracil daily
8	40 F	18 mths.	Moderate	+30%	20/12/43	13/1/44: +28 7/2/44: +2 21/6/44: Normal	7,600; 60%	21/1/44: 6,200, 55% 1/2/44: 3,600, 48% 5/2/44: 4,800, 44% 14/6/44: 6,000, 52% 4/10/44: 4,700, 61% 9/2/44: 3,300, 42% 23/2/44: 4,200, 52% 2/3/44: 5,600, 51% 11/3/44: 14,200, 51%	14 lb.	Partial thyroidectomy on 2/2/43, followed by recurrence of symptoms of thyrotoxicosis. Papular rash, chiefly on face, for 1 week, did not necessitate omitting treatment. Thiouracil stopped on 24/5/44
9	40 F	1 yr.	Severe	+52%	6/1/44	25/1/44: +17 21/6/44: +5	4,400; 45%	21/1/44: 6,200, 55% 1/2/44: 3,600, 48% 5/2/44: 4,800, 44% 14/6/44: 6,000, 52% 4/10/44: 4,700, 61% 9/2/44: 3,300, 42% 23/2/44: 4,200, 52% 2/3/44: 5,600, 51% 11/3/44: 14,200, 51%	22 lb.	Goitre increased for a time; went back to previous size on reducing the dose of thiouracil. No treatment since 4/10/44
10	32 F	4 mths.	"	+67%	14/2/44	8/2/44: +63 2/3/44: +10 5/7/44: +12 16/3/44: +33 28/3/44: +22 13/4/44: -7 25/7/44: +17	6,200; 32%	21/1/44: 6,200, 55% 1/2/44: 3,600, 48% 5/2/44: 4,800, 44% 14/6/44: 6,000, 52% 4/10/44: 4,700, 61% 9/2/44: 3,300, 42% 23/2/44: 4,200, 52% 2/3/44: 5,600, 51% 11/3/44: 14,200, 51%	14 lb.	No treatment required since 5/7/44
11	21 F	3 "	"	+75%	1/3/44	16/3/44: +33 28/3/44: +22 13/4/44: -7 25/7/44: +17	11,100	21/1/44: 6,200, 55% 1/2/44: 3,600, 48% 5/2/44: 4,800, 44% 14/6/44: 6,000, 52% 4/10/44: 4,700, 61% 9/2/44: 3,300, 42% 23/2/44: 4,200, 52% 2/3/44: 5,600, 51% 11/3/44: 14,200, 51%	6 lb.	At one time weight up by 23 lb.; neck much increased in size, and mild myxoedema. Relieved by adjusting dose of thiouracil. No treatment since 1/9/44
12	49 F	Over 5 yrs.	Moderate	+36%	5/3/44	17/10/44: +13	—	20/3/44: 6,800, 58% 30/8/44: 7,500	4 lb.	Congestive heart failure and auricular fibrillation dealt with first, before the initial B.M.R. and thiouracil treatment. Thiouracil omitted 2/8/44
13	23 F	2 mths.	Severe	+63%	16/3/44	20/5/44: +10	7,600; 47%	17/4/44: 6,000, 53% 5/7/44: 11,000, 48% 7/9/44: 12,000, 52% 18/4/44: 7,600, 54% 17/6/44: 7,300, 45% 4/8/44: 5,000, 65% 30/8/44: 4,000 13/10/44: 6,600, 71% 18/4/44: 8,800, 51% 14/6/44: 10,800, 59% 19/5/44: 4,000, 38% 7/9/44: 3,800, 33% 4/10/44: 3,800, 36% 6/6/44: 3,300, 69% 13/6/44: 4,500, 71% 4/8/44: 4,800, 71% 1/11/44: 7,600, 68% 28/6/44: 6,400, 54% 24/7/44: 5,000, 59% 9/8/44: 5,600, 59% 8/9/44: 5,900, 44% 20/9/44: 5,900, 48% 1/11/44: 5,600, 55% 29/6/44: 9,000, 68% 30/8/44: 6,900 12/10/44: 5,800, 67% 12/7/44: 7,800, 54% 4/10/44: 9,000, 69%	8 lb.	No treatment required since 5/9/44
14	43 F	6 "	Moderate	+38%	30/3/44	14/4/44: +26 30/4/44: +18 17/8/44: +7	9,069	17/4/44: 6,000, 53% 5/7/44: 11,000, 48% 7/9/44: 12,000, 52% 18/4/44: 7,600, 54% 17/6/44: 7,300, 45% 4/8/44: 5,000, 65% 30/8/44: 4,000 13/10/44: 6,600, 71% 18/4/44: 8,800, 51% 14/6/44: 10,800, 59% 19/5/44: 4,000, 38% 7/9/44: 3,800, 33% 4/10/44: 3,800, 36% 6/6/44: 3,300, 69% 13/6/44: 4,500, 71% 4/8/44: 4,800, 71% 1/11/44: 7,600, 68% 28/6/44: 6,400, 54% 24/7/44: 5,000, 59% 9/8/44: 5,600, 59% 8/9/44: 5,900, 44% 20/9/44: 5,900, 48% 1/11/44: 5,600, 55% 29/6/44: 9,000, 68% 30/8/44: 6,900 12/10/44: 5,800, 67% 12/7/44: 7,800, 54% 4/10/44: 9,000, 69%	4 lb.	Tachycardia of 100 per min. persists. Now on 0.1 g. of thiouracil daily
15	27 F	2 "	Mild	+23%	8/4/44	20/5/44: +10	6,200; 47%	17/4/44: 6,000, 53% 5/7/44: 11,000, 48% 7/9/44: 12,000, 52% 18/4/44: 7,600, 54% 17/6/44: 7,300, 45% 4/8/44: 5,000, 65% 30/8/44: 4,000 13/10/44: 6,600, 71% 18/4/44: 8,800, 51% 14/6/44: 10,800, 59% 19/5/44: 4,000, 38% 7/9/44: 3,800, 33% 4/10/44: 3,800, 36% 6/6/44: 3,300, 69% 13/6/44: 4,500, 71% 4/8/44: 4,800, 71% 1/11/44: 7,600, 68% 28/6/44: 6,400, 54% 24/7/44: 5,000, 59% 9/8/44: 5,600, 59% 8/9/44: 5,900, 44% 20/9/44: 5,900, 48% 1/11/44: 5,600, 55% 29/6/44: 9,000, 68% 30/8/44: 6,900 12/10/44: 5,800, 67% 12/7/44: 7,800, 54% 4/10/44: 9,000, 69%	Nil	Had a partial thyroidectomy in 1936. Treatment omitted 5/9/44
16	72 F	8 yrs.	"	+21%	8/5/44	22/5/44: +7	5,200; 45%	17/4/44: 6,000, 53% 5/7/44: 11,000, 48% 7/9/44: 12,000, 52% 18/4/44: 7,600, 54% 17/6/44: 7,300, 45% 4/8/44: 5,000, 65% 30/8/44: 4,000 13/10/44: 6,600, 71% 18/4/44: 8,800, 51% 14/6/44: 10,800, 59% 19/5/44: 4,000, 38% 7/9/44: 3,800, 33% 4/10/44: 3,800, 36% 6/6/44: 3,300, 69% 13/6/44: 4,500, 71% 4/8/44: 4,800, 71% 1/11/44: 7,600, 68% 28/6/44: 6,400, 54% 24/7/44: 5,000, 59% 9/8/44: 5,600, 59% 8/9/44: 5,900, 44% 20/9/44: 5,900, 48% 1/11/44: 5,600, 55% 29/6/44: 9,000, 68% 30/8/44: 6,900 12/10/44: 5,800, 67% 12/7/44: 7,800, 54% 4/10/44: 9,000, 69%	7 lb.	Thyrotoxicosis of long standing. B.M.R. known to have been +54 in 1939. Treatment omitted 4/10/44
17	52 F	15 "	Severe	+35%	25/5/44	7/6/44: +27 26/6/44: +7	7,000; 70%	17/4/44: 6,000, 53% 5/7/44: 11,000, 48% 7/9/44: 12,000, 52% 18/4/44: 7,600, 54% 17/6/44: 7,300, 45% 4/8/44: 5,000, 65% 30/8/44: 4,000 13/10/44: 6,600, 71% 18/4/44: 8,800, 51% 14/6/44: 10,800, 59% 19/5/44: 4,000, 38% 7/9/44: 3,800, 33% 4/10/44: 3,800, 36% 6/6/44: 3,300, 69% 13/6/44: 4,500, 71% 4/8/44: 4,800, 71% 1/11/44: 7,600, 68% 28/6/44: 6,400, 54% 24/7/44: 5,000, 59% 9/8/44: 5,600, 59% 8/9/44: 5,900, 44% 20/9/44: 5,900, 48% 1/11/44: 5,600, 55% 29/6/44: 9,000, 68% 30/8/44: 6,900 12/10/44: 5,800, 67% 12/7/44: 7,800, 54% 4/10/44: 9,000, 69%	11 lb.	Had radium treatment in 1934. Moderate tachycardia persists. Now on 0.1 g. thiouracil daily
18	52 F	18 mths.	Very severe	+71%	16/6/44	3/7/44: +78 24/7/44: +65 7/9/44: +58 4/10/44: +34	6,200; 46%	17/4/44: 6,000, 53% 5/7/44: 11,000, 48% 7/9/44: 12,000, 52% 18/4/44: 7,600, 54% 17/6/44: 7,300, 45% 4/8/44: 5,000, 65% 30/8/44: 4,000 13/10/44: 6,600, 71% 18/4/44: 8,800, 51% 14/6/44: 10,800, 59% 19/5/44: 4,000, 38% 7/9/44: 3,800, 33% 4/10/44: 3,800, 36% 6/6/44: 3,300, 69% 13/6/44: 4,500, 71% 4/8/44: 4,800, 71% 1/11/44: 7,600, 68% 28/6/44: 6,400, 54% 24/7/44: 5,000, 59% 9/8/44: 5,600, 59% 8/9/44: 5,900, 44% 20/9/44: 5,900, 48% 1/11/44: 5,600, 55% 29/6/44: 9,000, 68% 30/8/44: 6,900 12/10/44: 5,800, 67% 12/7/44: 7,800, 54% 4/10/44: 9,000, 69%	28 lb.	Rather resistant to treatment. In all was an in-patient for 11 weeks. Auricular fibrillation which was present restored to normal rhythm with quinidine. Now on 0.1 g. thiouracil daily
19	40 M	2 yrs.	Moderate	+39%	18/6/44	12/7/44: +17 25/10/44: -7	6,700; 44%	17/4/44: 6,000, 53% 5/7/44: 11,000, 48% 7/9/44: 12,000, 52% 18/4/44: 7,600, 54% 17/6/44: 7,300, 45% 4/8/44: 5,000, 65% 30/8/44: 4,000 13/10/44: 6,600, 71% 18/4/44: 8,800, 51% 14/6/44: 10,800, 59% 19/5/44: 4,000, 38% 7/9/44: 3,800, 33% 4/10/44: 3,800, 36% 6/6/44: 3,300, 69% 13/6/44: 4,500, 71% 4/8/44: 4,800, 71% 1/11/44: 7,600, 68% 28/6/44: 6,400, 54% 24/7/44: 5,000, 59% 9/8/44: 5,600, 59% 8/9/44: 5,900, 44% 20/9/44: 5,900, 48% 1/11/44: 5,600, 55% 29/6/44: 9,000, 68% 30/8/44: 6,900 12/10/44: 5,800, 67% 12/7/44: 7,800, 54% 4/10/44: 9,000, 69%	12 lb.	Frequent extrasystoles before treatment; almost disappeared after it. Now on 0.05 g. thiouracil daily
20	26 F	6 mths.	Mild	+23%	26/6/44	17/7/44: +14	8,000; 57%	17/4/44: 6,000, 53% 5/7/44: 11,000, 48% 7/9/44: 12,000, 52% 18/4/44: 7,600, 54% 17/6/44: 7,300, 45% 4/8/44: 5,000, 65% 30/8/44: 4,000 13/10/44: 6,600, 71% 18/4/44: 8,800, 51% 14/6/44: 10,800, 59% 19/5/44: 4,000, 38% 7/9/44: 3,800, 33% 4/10/44: 3,800, 36% 6/6/44: 3,300, 69% 13/6/44: 4,500, 71% 4/8/44: 4,800, 71% 1/11/44: 7,600, 68% 28/6/44: 6,400, 54% 24/7/44: 5,000, 59% 9/8/44: 5,600, 59% 8/9/44: 5,900, 44% 20/9/44: 5,900, 48% 1/11/44: 5,600, 55% 29/6/44: 9,000, 68% 30/8/44: 6,900 12/10/44: 5,800, 67% 12/7/44: 7,800, 54% 4/10/44: 9,000, 69%	6 lb.	Transient irritating papular rash; disappeared on reducing dose of thiouracil. Now on 0.05 g. daily

TABLE OF RESULTS (*continued*)

A	B	C	D	E	F	G	H	I	J	K
21	52 F	2 yrs.	Severe	+47%	10/7/44	28/7/44: +22 18/8/44: +14	3,400; 47%	24/7/44: 5,000, 57% 9/8/44: 5,400, 53% 20/9/44: 4,600, 61% 1/11/44: 6,800, 71% 1/8/44: 4,500, 44% 6/9/44: 6,900 4/10/44: 5,800, 38%	7 lb.	Auricular fibrillation, which was present, reverted to normal rhythm while under treatment with thiouracil. Now on 0.1 g. daily
22	45 F	9 mths.	"	+29%	14/7/44	3/8/44: +26 19/9/44: +9	4,400; 61%		4½ lb.	Case judged to be severe on clinical grounds. Irritation of skin on arms and legs. Later slight eczematous eruption confined to hands. Now on 0.05 g. of thiouracil daily
23	42 F	? 7 yrs.	"	+48%	1/8/44	10/8/44: +16	2,800; 56%	15/8/44: 4,700, 38% 7/9/44: 5,500, 68% 26/8/44: 6,400, 49% 26/9/44: 7,700, 62% 27/10/44: 6,200, 53% 10/10/44: 5,200, 38% 20/10/44: 5,000, 51%	6 lb.	W.B.C. rose with treatment. Now on 0.1 g. of thiouracil daily
24	22 F	2 mths.	Moderate	+41%	14/8/44	30/8/44: +7	4,800; 58%		17 lb.	Treatment omitted 1/11/44
25	21 F	2 "	"	+36%	4/9/44	28/9/44: +21 27/10/44: +12 19/10/44: +17	7,600; 72%		6 lb.	Now on 0.2 g. of thiouracil daily
26	45 F	2 "	Severe	+50%	2/10/44		3,600; 40%		8 lb.	Rapid clinical response to thiouracil. Now on 0.2 g. daily. Rise in W.B.C. with treatment
27	29 F	4 "	"	+64%	13/10/44	28/10/44: +24	6,600; 40%	24/10/44: 7,800, 48%	8½ lb.	Able to leave hospital after a fortnight, much improved. Now on 0.2 g. thiouracil b.d.

Key to Table.—A: Case number. B: Age and sex. C: Duration of illness. D: Degree of thyrotoxicosis. E: % of B.M.R. above normal. F: Date of starting treatment with thiouracil. G: Later B.M.R. readings. H: Initial total white cell count and % of polymorphs. I: Later white cell counts and % of polymorphs. J: Gain in weight. K: Remarks.

for at least a month before thiouracil was administered. With the exception of Nos. 3, 6, and 18, who were seriously ill at the beginning of their treatment, strict confinement to bed was not practised.

During the initial in-patient phase the dose of thiouracil was generally 0.2 g. t.d.s. Three early cases also had thiourea in doses of 1 g. t.d.s. before thiouracil became available. Thus No. 2 received 52 g. of the substance and No. 3 had 35 g. No. 1, after only 7 g. of thiourea, developed toxic symptoms resembling those described by St. Johnston (1944), including extensive skin eruption, vomiting, headache, and fever. She was subsequently given thiouracil, when a much milder maculopapular rash appeared on the parts of the skin exposed to light. The rash disappeared after the dose was reduced, and eventually she did exceptionally well. Skin rashes were caused by thiouracil in a few other instances. No. 8 had a papular eruption on the face, lasting one week, which cleared up of its own accord without having to modify the treatment. No. 20 had a transient papular rash which disappeared after the dose of thiouracil was reduced. No. 22 complained of occasional itching of the limbs, at first without any actual skin changes; later the parts exposed to light showed a scaly erythematous eruption, and it was interesting to note that as soon as she began to wear stockings the skin of the legs cleared rapidly, while the lesions of the hands and wrists disappeared much more slowly with a reduction in the dose of thiouracil. Only in No. 22 was there a moderate degree of leucopenia while the rash was present.

Signs of improvement were usually apparent 10 to 14 days after starting treatment. Severe thyrotoxicosis frequently responded to thiouracil as quickly as the moderate type, but in some of the former—e.g., Nos. 5, 17, and 18—one sometimes had to persevere for several weeks before the patients began to show a change for the better. Restlessness was usually the first to go, and then the flushed and moist skin would become paler and drier. The staring expression and the shiny appearance of the eyes, which are such striking features of thyrotoxicosis, would fade, the weight would begin to go up, and the tremor of the fingers would become less. Then the vascularity of the thyroid would diminish, as shown by lessening or disappearance of the bruit over the gland; and finally the tachycardia would subside. Oddly enough, it was in the milder cases—e.g., Nos. 7 and 14—that tachycardia tended to persist longest. In every instance, with the exception of No. 6, the patient would admit to feeling better after a few weeks' treatment, and all those gainfully employed previous to their illness were back at work long before it would have been possible had they had a partial thyroidectomy. Reduction of the B.M.R. was roughly parallel in each case with signs of clinical improvement. In nearly all patients the B.M.R. came down to within normal limits. Only in Nos. 6 and 19 has this not been achieved. In No. 6 the period available for treatment was probably too short, while in No. 19 it is almost certainly a matter of time before a normal basal metabolic rate is reached. Exophthalmos, which was present in only a few of the patients, was not appreciably influenced by treatment; neither did enlargement of the thyroid diminish to any extent. Four

instances of auricular fibrillation were noted, two of which—Nos. 4 and 21—reverted to normal rhythm spontaneously in the course of the treatment, and another—No. 18—in whom this was achieved by means of quinidine. In the fourth—No. 12—auricular fibrillation persists, and owing to the fact that it is probably of at least 5 years' standing no attempt at conversion to normal rhythm with quinidine was made. The gain in weight was negligible in a few, appreciable in the majority, and in two it amounted to almost 2 st. since starting treatment. Only No. 3 lost weight. Excessive gain was sometimes accompanied by a bloated appearance, listlessness, and an increase in size of the thyroid gland. In contrast to the view held by Himsworth, I could see no difference at all between these manifestations and mild myxoedema. By a suitable reduction of the dose of the drug it was possible rapidly to reverse the pathological depression of metabolism, the excessive increase in weight, and the enlargement of the neck. The size of the neck was recorded in each case and checked at regular intervals, this proving an additional guide to the dose of thiouracil required. In fact, experience showed that the maintenance dose on which the pulse rate and general condition remained satisfactory varied from individual to individual, thus proving the value of periodic inspection. All patients were seen regularly after discharge—first at 2, then at 3, and finally at 4 weeks' intervals. There was only one patient—No. 3—who did not co-operate satisfactorily. She turned up only twice after discharge from hospital and ceased taking thiouracil of her own accord after 3 months. She was seen again in May, 1944, when her condition was found to have remained satisfactory and the B.M.R. was +10. More recently this patient came up again with symptoms of a slight recurrence of thyrotoxicosis, and her treatment was resumed.

As for the maintenance dose, the patients were usually given 0.2 g. of thiouracil, b.d., for 2 to 4 weeks after leaving hospital. Later, most of them were maintained on 0.2 g. and some on 0.1 or 0.05 g. daily. In a few instances it was found possible to omit treatment altogether—e.g., in No. 8 since May 24, 1944, No. 10 since July 5, 1944, No. 12 since Aug. 2, 1944, No. 13 since Sept. 5, 1944, No. 15 since Sept. 5, 1944, and No. 16 since Oct. 24, 1944. In No. 5, treatment had to be resumed because the man began to lose ground once more, and the same had to be done in No. 1 after omitting treatment for 3 months. Astwood (1943) mentions a patient in whom, after a relatively short period of treatment, he omitted thiouracil for a few weeks and had to resume it because of a recurrence of symptoms. Himsworth (1944) reported that in 3 mild cases he was able to leave off thiouracil for periods of from 7 weeks to 7 months.

Observations on the white cell count proved interesting. With the exception of Nos. 1–6 and 12, a preliminary count was always made before treatment was started, and low initial readings were not at all infrequent. These, although sometimes bordering on frank leucopenia, were not taken to be a bar to giving thiouracil, and surprisingly in those the white cell count usually showed a rise as the treatment proceeded. In no case was there an alarming fall of the white cell or polymorph count. Consistently low figures were seen only in Nos. 4 and 16. In this connexion it is worth noting the findings of

Goldsmith and associates (1944), that when liver extract is given to rats simultaneously with thiourea it protected them from neutropenia.

Three patients had operations of partial thyroidectomy before they came under the present review. No. 6, operated on 18 years before, had a nodular goitre, and a recurrence of symptoms 9 years after operation. About 12 months before coming to hospital she became short of breath, experienced nausea and vomiting, and when admitted her heart showed marked enlargement to the left and a systolic murmur at the apex. She showed no appreciable response after 4 weeks' treatment, and, unfortunately, although she was urged to stay, insisted on going home. It was reported later that she had died suddenly 3 weeks after leaving hospital. In No. 8, in which partial thyroidectomy failed to cure the condition, 5 months' treatment with thiouracil appeared to complete what surgery had left undone. Another milder recurrence, 8 years after partial thyroidectomy—No. 15—did equally well. No. 17, radium treatment of which 10 years before had been a complete failure, responded satisfactorily to thiouracil.

Conclusion

We have now in thiouracil a potent weapon for overcoming thyrotoxicosis. The drug, although not entirely devoid of risks, is much safer than operation. All patients suffering from thyrotoxicosis should therefore be given thiouracil. At some future date it may be possible to assess the initial and maintenance dosages on a more scientific basis, but at present, in the light of experience, a satisfactory working rule is to give 0.2 g. of thiouracil thrice daily for the first 3 to 5 weeks, after which the dose should be gradually reduced, and kept at the lowest possible level compatible with the patient's well-being. Slow response to treatment calls for patience, and not for increasing the dose beyond a safe limit. Leucopenia before the treatment should not be taken as a contraindication to the use of thiouracil. All patients treated with thiouracil should be kept under adequate supervision. Only more prolonged observations will tell whether thiouracil is capable of effecting a permanent cure within a measurable period.

Summary

A series of 27 unselected cases of thyrotoxicosis treated with thiouracil for periods varying from 3 weeks to 12 months are described.

Good response, with the exception of one long-standing instance, was noted in all.

The importance of continued supervision of the treatment is stressed.

It is submitted that the hitherto almost unrivalled surgical treatment of thyrotoxicosis may, in the light of further experience, have to give way to medical treatment.

Grateful thanks are due to both my medical and my surgical colleagues, who kindly passed on to me their patients with thyrotoxicosis, and thus made this series much larger than it would otherwise have been. Our biochemist, F. Morton, M.Sc., F.R.I.C., carried out the B.M.R. estimations, and Messrs. British Drug Houses generously supplied, free of charge, most of the thiouracil used in this investigation.

REFERENCES

- Astwood, E. B., Sullivan, J., Bissell, A., and Tyslowitz, R. (1943). *Endocrinology*, **32**, 210.
 — (1943). *J. Amer. med. Ass.*, **122**, 78.
 Campbell, D., Landgrebe, F. W., and Morgan, T. N. (1944). *Lancet*, **1**, 630.
 Gabrilove, J. L., and Kert, M. J. (1943). *J. Amer. med. Ass.*, **124**, 504.
 Goldsmith, E. D., Gordon, A. S., Finkelstein, G., and Charipper, H. A. (1944). *Ibid.*, **125**, 847.
 Himsworth, H. P. (1943). *Lancet*, **2**, 465.
 — Sharpey-Schafer, E. P., Evans, H., and Joll, C. (1944). *British Medical Journal*, **1**, 852.
 Kennedy, T. H. (1942). *Nature*, **150**, 233.
 Mackenzie, C. G., and Mackenzie, J. B. (1943). *Endocrinology*, **32**, 185.
 Mackenzie, J. B., Mackenzie, C. G., and McCollum, E. V. (1941). *Science*, **94**, 518.
 Newcomb, P. B., and Deane, E. W. (1944). *Lancet*, **1**, 179.
 Richter, C. P., and Clisby, K. H. (1941). *Proc. Soc. exp. Biol.*, N.Y., **48**, 864.
 — (1942). *Arch. Path.*, **33**, 46.
 St. Johnston, C. R. (1944). *Lancet*, **2**, 42.
 Williams, R. H., and Bissell, G. W. (1943). *New Engl. J. Med.*, **229**, 97.
 — Jandorf, B. J., and Kay, G. A. (1944a). *J. lab. clin. Med.*, **29**, 329.
 — Weinglass, A. R., and Kay, G. A. (1944b). *Amer. J. med. Sci.*, **207**, 701.

M. J. MacNeal and M. C. Place (*Amer. J. Dis. Child.*, 1944, **68**, 30) record a case of fulminating meningococcaemia in a boy aged 8 years, who recovered after treatment first with sulphadiazine intravenously and later with the calcium salt of penicillin intravenously and intramuscularly.

THE HAEMOGLOBIN LEVEL IN MUNICIPAL-SCHOOL CHILDREN

EFFECT OF IRON THERAPY, SCHOOL DINNERS, AND SEASON

BY

R. H. DOBBS, M.D., M.R.C.P.

Major, R.A.M.C.

HELEN M. M. MACKAY, M.D., F.R.C.P.

Member of the Staff of the Medical Research Council

(Physicians to the Queen Elizabeth Hospital for Children, London)

AND

K. BINGHAM

Assistant, Pathological Department, Royal Free Hospital

The lack of knowledge of normal haemoglobin levels in school-children, of the physiological rise with age, and of the effects of iron therapy, diet, and economic circumstances has recently aroused attention in this country. The present paper represents an effort, only partially successful, to increase our knowledge of this subject.

Clinical Material

Children at two municipal schools were examined. One—school B—was in a London suburb, where 127 children, aged 7 to 12 years, were examined in Oct., 1942. Many of the pupils' fathers were black-coated workers in moderately comfortable circumstances. The other—school A—was in a small town near London where the children had repeated haemoglobin examinations during a period of over a year, beginning early in 1942. The number of children examined at this school was 325. Here economic standards were more varied, but very few families were below the poverty line, as shown by the supply of free milk or free dinners. About half the fathers were industrial or transport workers (mechanics, skilled craftsmen, unspecified munition workers, railway workers, etc.); about 23% were in the armed Forces, and another 13% were clerical workers or shop-assistants. About 43% of the mothers did paid work, part- or full-time, outside their own homes.

Technique, and Some Sources of Error

Estimations were made with a Haldane standard by the three of us, and figures are given with the National Physical Laboratory B.S.I. corrections applied for colour tube and pipettes. Apart from the percentage correction for the dilution tubes (a correction required because the distance between the 20 and 140 marks, and hence the diameter, differed from the B.S.I. standard), the mean N.P.L. correction for the tubes was -0.3 at 80%. This correction was obviously negligible, and was omitted. The maximum correction thus omitted on any one dilution tube was -0.9 at 80%. The blood was taken from a prick in the thumb after soaking the hand in hot water. The earliest estimations were made during a period of extremely cold weather in January and early February of 1942. The children at the time nearly all had chilled extremities, and, in spite of soaking the hand in hot water, there were wide discrepancies in the results, presumably because of capillary changes and stasis. All readings taken during this period have been discarded as doubtful. It is probable that cold limbs, in spite of precautions to get a warm hand and a free flow of blood, produced inaccurate estimations at other periods, but it is difficult to see how this can be prevented under the conditions of field work. Another source of misleading results is, we believe, anxiety or apprehension on the part of the child: it was noticed that children showing anxiety often registered wide fluctuations in haemoglobin level.

Haemoglobin Level in Relation to Age and Sex

Table I shows that there was a fairly steady rise in haemoglobin level with age, though the numbers in the different subdivisions were not sufficient to even out chance fluctuations. Taking the mean haemoglobin level for the combined results at school A in Feb., 1942, and again in Feb. or March, 1943, together with school B in Oct., 1942, there was a rise from 87.8% at 7 years to 92.1% at 10 years—that is, a rise of 4.3 in three years, or an average rise of 1.4 per year of age; and each subdivision in Table I shows a rise with age of a similar order. The haemoglobin levels at school B were slightly