THIOURACIL IN THE TREATMENT OF THYROTOXICOSIS

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From the great sequence of workers from Astwood in 1943 to Leys in 1945 there has come a practically unbroken chorus of praise for the good effects of thiourea, thiouracil, and methyl thiouracil in the treatment of thyrotoxicosis; there are, however, some few (Joll; Morley, 1944) who are not entirely of that mind. To this more critical view we ourselves would incline, while fully realizing the great value of thiouracil in the treatment of most cases of thyrotoxicosis. We therefore present a series of 29 cases observed and measured by us, mostly over a period of 16 to 21 months, whereas other workers (Nussey, 1944) include some much shorter observations. We believe that this longer period is of great importance, as in several cases we have seen initial improvement, comparable to that obtained with Lugol's iodine, followed by later relapse while still under treatment; and, in some instances, leading to thyroidectomy.

Our Series of Cases

In all, 29 cases are here studied—8 men and 21 women—the ages varying from 22 to 66 years. The evidence of thyrotoxicosis, suggested by the symptoms, has in each case been supported by a raised basal metabolic rate. The division into primary and secondary types has so much bearing on our main argument that some explanation is necessary: the former have developed their

usual dosage of thiouracil has been 0.5 g. twice daily until the B.M.R. began to return to normal limits; then 0.2 g. daily or twice daily; and finally 0.05–0.19 g. as a maintenance dose. The figures given (see Table) of the time under treatment refer only to the actual days on which the patient took the drug and do not include periods of investigation or of rest (often lasting for weeks). From this table of results the following broad inferences have been drawn.

Improvement was noted in 22 cases, irrespective of sex and age but not of duration; the tendency was, the longer the history the less the effect of thiouracil. Of these 22 cases, 12 could be classed as much improved, mainly in a clinical sense, although there was a corresponding march in physico-chemical changes, most notably in B.M.R. Three cases were so little improved as to require thyroidectomy, and in all three it will be noted that the thyrotoxicosis was of secondary type. Of the 21 primary cases recorded above improvement occurred in 19; of the 8 secondary cases, improvement took place in 2 only.

Effects on the Thyroid Gland

Enlargement.—In those cases with marked goitre further enlargement of the thyroid gland was noted after the 7th day—which constituted the peak period—afterwards declining to a

FIG. 1.—Case 14816. Photomicrograph of section of thyroid gland. ($\times 175$.)

symptoms and signs either before the appearance of a goitre or *pari passu*; the latter are regarded as secondary to an established goitre, often of years' duration.

Thiouracil was used almost exclusively—first while the patient was in hospital, until the B.M.R. returned to normal, and then as an out-patient practice. Of the physico-chemical measurements made, initial and end readings alone are given; in all B.M.R. estimations the Benedict spirometer was used; blood sugar and cholesterol levels were determined weekly, but we cannot agree with Leys that they are anything like so useful as the B.M.R. as a guide to the degree of thyrotoxicosis. Our

FIG. 2.—Case 14766. Photomicrograph of section of thyroid gland. ($\times 175$.) (Photos by E. L. Murray, A.R.P.S.)

size somewhat above that before treatment. In one case (No. 26) the neck enlarged from 31.4 cm. to 36.2 cm. and remained at that girth long after all symptoms had gone and physico-chemical measurements had returned to normal.

Microscopical Appearance.—In 2 cases we have had an opportunity of examining sections of the thyroid gland removed at operation, undertaken because of the failure of response to thiouracil. Photomicrographs (Figs. 1 and 2) are here shown, and the pathologist (C. V. Harrison) reported as follows:

"14816.—Macroscopically, the thyroid was enlarged and nodular, and showed plentiful colloid. Some of the nodules showed signs of

Table of Results

Case No.	Sex	Age	Type and Duration of Lesion	Thiouracil		A. Weight B. Pulse C. B.P.	Mg./100 c.cm. in Blood of A. Sugar B. Cholesterol	B.M.R.	Remarks
				A, Days on Drug B. Grammes	I.P. O.P.				
1	F.	24	Primary, 1 year	A, 35 B, 7.5	31 6	A, 127-128½ lb. B, 70-52 C, 130/70-110/60	A, 94-86 B, 98-85	+19% to -2%	Improved. Fibrillation. No recurrence after 18 months
2	F.	22	Primary, 3 months	A, 24 B, 6.5	— —	A, 96-98½ lb. B, 92-80 C, 120/80-95/75	A, 123-82 B, 133-208	+28% to -11%	Improved. Recurrence after 14 months without treatment
3	F.	50	Primary, 1 year	A, 26 B, 7.5	30 5.5	A, 118½-114½ lb. B, 88-72 C, 158/85-110/80	A, 127-91 B, 95-103	+26% to +7%	Improved. No recurrence after 16 months
4	F.	26	Primary, 18 months	A, 25 B, 10.5	— —	A, 122½-129½ lb. B, 100-68 C, 145/65-110/60	A, 83-103 B, 74-130	+27% to +4%	Improved. No recurrence after 17 months
5	M.	57	Primary, 7 months	A, 10 B, 6	107 31.5	A, 110-130 lb. B, 110-78 C, 140/90-130/80	A, 92-105 B, 150-220	+42% to +7%	Much improved
6	F.	66	Primary, 7 months	A, 51 B, 11	40 8	A, 114½-115 lb. B, 108-72 C, 200/100-185/90	A, 68-109 B, 165-180	+34% to +3%	Improved
7	F.	30	Primary, 7 months	A, 46 B, 37.5	78 12.5	A, 122-134 lb. B, 84-88 C, 130/80-125/75	A, 80-82 B, 130-137	+31% to +9%	Improved
8	M.	40	Primary, 3 months	A, 44 B, 71.5	80 9.6	A, 127-134 lb. B, 94-80 C, 135/90-125/80	A, 76-96 B, 85-88	+23% to +1%	Improved
9	M.	54	Primary, 4 months	A, 38 B, 84	197 72.4	A, 145-152 lb. B, 90-78 C, 120/65-120/75	A, 68-105 B, 193-196	+25% to +9%	Improved
10	M.	40	Primary, 6 months	A, 45 B, 33	130 18.5	A, 156-183½ lb. B, 100-78 C, 145/75-120/60	A, 103-78 B, 75-220	+49% to +7%	Very much improved
11	M.	28	Primary, 2 months	A, 18 B, 18	268 126	A, 128-165 lb. B, 120-60 C, 190/100-115/70	A, 109-75 B, 72-155	+36% to +4%	Much improved
12	F.		Post-thyroidectomy Recurrence Secondary	A, 20 B, 9.6	40 13	A, 127-125 lb. B, 120-70 C, 160/70-100/60	A, 83-136 B, 162-96	+29% to -2%	Better
13	F.	23	Primary, 6 months	A, 32 B, 21	50 7.1	A, 94-152 lb. B, 96-68 C, 130/90-90/40	A, 86-74 B, 138-172	+51% to -3%	Much improved
14	F.	54	Primary, 1 year	A, — B, —	147 73	A, 132½-148 lb. B, 84-76 C, 120/90-130/70	A, 87-93 B, 130-142	+26% to +1%	Much improved
15	M.	34	Primary, 1 year	A, 17 B, 7	171 137	A, 121-126 lb. B, 104-73 C, 135/80-120/70	A, 122-91 B, 85-186	+26% to +4%	Improved
16	F.	37	Primary, 1 year	A, 19 B, 7.8	— —	A, 116½-114 lb. B, 94-88 C, 130/70-110/60	A, 103-98 B, 108-133	+42% to +37%	I.S.Q. Drug fever
17	M.	38	Primary, 18 months	A, 28 B, 28	56 14	A, 160-180½ lb. B, 88-74 C, 158/100-110/70	A, 88-72 B, 96-128	+34% to +3%	Much improved
18	F.	23	Primary, 1 year	A, 15 B, 12	40 8	A, 100-104 lb. B, 88-76 C, 140/70-130/75	A, 107-71 B, 108-133	+72% to +11%	Improved. Agranulocytosis
19	F.	51	Primary, 14 months	A, 90 B, 45	25 7	A, 77-92½ lb. B, 100-76 C, 190/70-120/75	A, 250-103 B, 122-207	+27% to +3%	Much improved
			Recurrence 6 months later	A, 29 B, 16.5	58 21.5			+30% to +7%	Remission on stopping treatment after 4 months
20	F.	44	Primary, 5 months	A, 33 B, 25.8	40 18.6	A, 98-103 lb. B, 88-72 C, 115/90-100/60	A, 75-72 B, 125-140	+38% to +4%	Better
21	M.	46	Primary, 8 months	A, 20 B, 9.5	75 28.4	A, 136-136½ lb. B, 98-76 C, 220/185-185/165	A, 81-84 B, 122-140	+30% to +8%	Improved
22	F.	43	Post-op. Recurrence 1 year Primary	A, 21 B, 8.4	186 74	A, 149-146 lb. B, 116-88 C, 150/80-130/80	A, 80-76 B, 103-202	+26% to +12%	I.S.Q.
23	F.	28	Secondary, 14 months	A, 38 B, 10.5	— —	A, 106-111 lb. B, 96-70 C, 110/70-110/80	A, 97-98 B, 122-78	+54% to +43%	I.S.Q.
24	F.	60	Secondary, 2 years	A, 33 B, 28	20 6.5	A, 102-104½ lb. B, 96-76 C, 170/85-130/65	A, 123-115 B, 80-82	+39% to +32%	I.S.Q. Marked neutropenia. Thyroidectomy
25	F.	44	Secondary, 3-4 years	A, 47 B, 17	— —	A, 91-94 lb. B, 96-66 C, 135/85-90/60	A, 96-75 B, 100-141	+32% to +2%	Little improved. Thyroidectomy
26	F.	49	Secondary	A, 30 B, 22	— —	A, 118-121½ lb. B, 88-76 C, 165/80-135/80	A, 148-127 B, 120-140	+47% to +39%	I.S.Q. Scarlatiniform rash

Table of Results (concluded)

Case No.	Sex	Age	Type and Duration of Lesion	Thiouracil		A, Weight B, Pulse C, B.P.	Mg./100 c.cm. in Blood of A, Sugar B, Cholesterol	B.M.R.	Remarks
				A, Days on Drug B, Grammes					
				I.P.	O.P.				
27	F.	23	Secondary	A, 10 B, 5	32 11.1	A, 86½-85½ lb. B, 78-70 C, 110/70-80/60	A, 187-250 B, 640-533	+19% to +10%	Slight improvement Thyroidectomy
28	F.	24	Secondary; recurrence following radium one year before	A, 28 B, 14	40 7	A, 137-140 lb. B, 80-70 C, 150/90-125/70	A, 105- 82 B, 87-164	+27% to -12%	Much improved
29	F.	38	Secondary, 18 months	A, — B, —	240 70	A, 118-126 lb. B, 120-84 C, 130/70-130/70	A, — B, —	— —	Much improved

degeneration. Microscopically, the gland is broken up into nodules by fibrous bands, but lymphocytic infiltration is minimal. The acini are variable in size, but are all in a resting stage with colloid storage. There is hyaline degeneration in the stroma between the acini.

14766.—Macroscopically, the gland was enlarged and nodular and contained plentiful colloid. Microscopically, the gland is broken up into nodules by bands of fibrous tissue. It shows quite numerous foci of lymphocytic infiltration, many with germinal centres. The thyroid acini are mostly enlarged and filled with colloid, and show a resting epithelium; only a few showed any signs of hyperplasia."

From the work of Moore *et al.* (1944) at the Massachusetts General Hospital on 34 cases treated with thiouracil as a pre-operative drug we know that the most prompt clinical response occurred in those patients whose thyroids, on histological examination, showed marked hyperplasia with a low colloid content. It is interesting to observe that those two cases of ours which responded badly to thiouracil both had thyroids in which involutionary changes predominated over hyperplasia.

Toxic Effects of Thiouracil

Symptomatic.—Although nausea and occasional vomiting were experienced in the earlier cases treated by us with thiourea, we have not seen this occur with thiouracil. The chief symptoms noted have been vasomotor—faintness, flushing, and vague muscular pains in the chest, head, and neck.

Granulocytopenia.—Nearly every case we have treated has shown an absolute granulocytopenia (of varying degree) with relative lymphocytosis, usually from the 7th to 10th day. When the white count falls to around 4,500 per c.mm. (with lymphocytes over 40%), cessation of the drug for 3 to 4 days is usually enough to cause the count to return to normal, and when this occurs the drug can be started again without untoward effects.

Agranulocytosis.—Only one of our cases (No. 18) developed a true agranulocytosis, although two others (Nos. 12 and 24) developed such severe neutropenia as to warrant active therapy. The striking fact in this case was the rate of development of the agranulocytosis; although blood counts were done on alternate days, the white count fell to *nil* in 24 hours. The cause would appear to be overdosage rather than a personal idiosyncrasy; because this girl began again with her thiouracil and has since had 20 g. without ill effects. This case is also of interest because the patient developed her agranulocytosis 23 days after treatment—contrary to Himsworth's general rule that such cases usually develop during the first 14 days. In all three cases extract of yellow bone-marrow given by mouth was found to be of most value in restoring the white count to normal.

Purpura.—Severe thrombocytopenic purpura has been described by Newcomb and Deane (1944). One of our cases, that of a female diabetic aged 58, developed a marked purpuric rash after 18 days' (16.5 g.) treatment with thiouracil. The blood picture was as follows: thrombocytes, 360,000 per c.mm.; coagulation time 5½ minutes; bleeding time, 9 minutes; Hess's test strongly positive. The condition abated on cessation of the drug.

Drug Fever.—St. Johnston (1944) has reported 3 cases of drug fever in his series of 7 cases treated with thiourea. In our series we have had one such case (No. 16). This patient, after 8 days' therapy (14 g.), began to complain of headache, nausea, painful glands in her neck, and sore mouth and eyes; her temperature rose to 102.2° F. and her pulse to 124. Her face was flushed, with numerous small white blebs over both cheeks, her eyelids were red and swollen, her mouth showed many small white ulcers, her submandibular and axillary glands were large and

shotty; there was no splenomegaly; the skin over her thorax and abdomen had a fine maculo-papular rash. Her white count at this time was 7,400 per c.mm., of which polymorphonuclear cells were 68%, lymphocytes 17%, monocytes 2%, and eosinophils 13%. On cessation of the drug the symptoms abated, but on starting again—on two separate occasions—the signs and symptoms returned. This case differs from those described in showing ulceration of the mouth, eosinophilia, and absence of both splenomegaly and neutropenia.

Other Rashes.—Several of our cases have shown rashes, which were of two main types—maculo-papular, as in the woman described above, and scarlatiniform (Case 26).

Effects of Thiouracil in Cases Other than of Thyrotoxicosis

Hypertension and Diabetes Mellitus.—On the basis of reduction both of blood pressure and of blood-sugar level in cases of thyrotoxicosis, we measured the effect of thiouracil on a group of cases suffering from these conditions. Six cases of essential hypertension were treated for varying periods with little or no response. Its value in diabetes is also disappointing, although we found that its use in diabetes with mild thyrotoxicosis allowed of a reduction in the amount of insulin formerly required.

Cardiac Failure.—Blumengart *et al.* have suggested subtotal thyroidectomy in severe cases of cardiac failure, on the assumption that by reduction of B.M.R. the work of the heart is diminished. On this principle we tried to decrease the activity of the thyroid in two cases of cardiac failure; one case was treated for 30 days (22 g.) with no apparent improvement. We reached the conclusion that thiouracil is of value only in those cases of cardiac failure which have a thyrotoxic basis. Cases of auricular fibrillation of thyrotoxic origin may be controlled by thiouracil with a return to a normal rhythm; this was seen in Cases 1 and 19.

Myxoedema.—In an attempt to discover the mode of action of thiouracil we gave it to a patient with myxoedema. She received 26 g. in 26 days. There was no change in her blood sugar or cholesterol levels, her B.M.R. rose from -40% to -37%, and she lost 4 oz. in weight.

Summary

Of 29 cases of thyrotoxicosis treated with thiouracil improvement was noted in 22, while 12 were classified as much improved.

Of the 21 cases of primary type, improvement was noted in 19, and of the 8 secondary types in 2 cases only.

The effects on the thyroid gland are discussed and photomicrographs after thyroidectomy shown.

Toxic effects are discussed.

The effects of thiouracil in cases other than thyrotoxicosis are recorded.

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