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EFFECT OF PRETREATMENT WITH METHYLTHIOURACIL ON RESULTS OF ^{131}I THERAPY

BY

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Little is known about the fundamental biological changes produced in thyroid cells when they are irradiated by radioactive iodine, and still less about factors which modify these changes. It might be expected that thyroid tissue would become more sensitive to ionizing radiations after treatment with antithyroid drugs which increase both the vascularity of the gland (Thomas, 1945) and the number of mitoses in thyroid cells (Řeřábek and Řeřábek, 1947). Indeed, Williams *et al.* (1949) in an uncontrolled trial had the impression that patients pretreated with propylthiouracil required a lower dose of ^{131}I than untreated cases. Furthermore, Fraser *et al.* (1954) devised a procedure which involved pretreatment by methylthiouracil and thyroxine and which was said to give more consistent results than the standard methods of ^{131}I administration. On the other hand, Chapman and Maloof (1955) and Blomfield *et al.* (1959) observed no consistent difference in the response of those which had received no pretreatment. Werner (1955), however, states that methylthiouracil produces a radioresistant gland.

Since ^{131}I produces its effects relatively slowly it is sometimes necessary to control thyrotoxicosis with antithyroid drugs before treatment with the radioisotope. Moreover, many patients are referred for this form of treatment who have previously received courses of antithyroid drugs. We decided, therefore, to carry out a trial to see whether pretreatment with methylthiouracil influenced the results of ^{131}I therapy.

We decided to use a simple clinical method for the assessment of the dose of ^{131}I which we would use. This is similar to that described by Macgregor (1957), and we report our experience using this procedure. Our results confirm and extend his conclusions.

Material and Methods

One hundred and fifty patients in whom the diagnosis of thyrotoxicosis had been confirmed by the clinical index, described by Crooks *et al.* (1959), and by ^{131}I studies were considered on the criteria laid down by Blomfield *et al.* (1955) to be suitable for ^{131}I therapy.

Since the method of assessment of dosage is subjective and the prescribing physician might have altered his criteria during the three and a half years over which the observations were spread, certain precautions were taken in the design of the investigation. The doses of ^{131}I given to the different groups of patients were prescribed by the same physician (J. C.), and the observations on pretreated cases were controlled by those on untreated cases over the same time intervals. Four groups were studied.

Group 1 consisted of 28 patients who had received methylthiouracil for periods ranging from three months to one year. Administration of the drug ceased one week before treatment with ^{131}I. At this time all the subjects were either euthyroid or minimally thyrotoxic.

Group 2 consisted of 45 patients who had been treated with ^{131}I over the same period as Group 1, and who had never received an antithyroid drug.

When it became clear that methylthiouracil conferred some degree of radioresistance on the thyroid gland two further groups were studied.

Group 3 consisted of 21 patients previously treated with methylthiouracil in the same way as those in group 1 but in whom the dose estimated in the standard manner was arbitrarily increased by 25%.

Group 4 acted as the control to group 3. It included 56 patients who were not pretreated and whose dose was determined in the same way as that of patients in groups 1 and 2. They differed from group 2 only in the fact that they were treated contemporaneously with group 3.

All cases, with the exception of a few who were treated early in the course of the investigation, were given tracer doses of ^{131}I during the week before treatment in order to determine the 48-hour gland uptake of ^{131}I. In patients who had been receiving methylthiouracil the drug was stopped 48 hours before the tracer dose was administered.

Method of Dose Estimation

The basic principle of dose estimation used was that small doses were prescribed for patients with small glands and large doses for patients with large glands. It was decided from a review of the results of other workers that patients with impalpable glands would be given doses of 4–5 mc., those with minimal but definite diffuse enlargement of the gland 6–7 mc., and patients with larger glands doses from 7–25 mc. according to the size of the goitre. Many other factors besides gland size influenced the dose prescribed: for example, post-thyroidectomized patients were given 5–6 mc., unless the gland remnant was exceptionally large. Relatively high doses were given to patients with nodular glands, cardiac

failure, and uncontrolled diabetes mellitus, or whenever the risk of producing hypothyroidism was less than the need for a rapid remission of symptoms.

While each patient was being examined with a view to dose prescription the size of the gland was estimated in grammes, though the inaccuracies of this estimate are fully appreciated. This was done in order to obtain, *after each patient had been treated*, the dose which would have been given if the formula for dose prescription given by Blomfield *et al.* (1955) had been used. This formula is

$$\text{Dose in rads* per mc.} = \frac{805 \times \text{48-hour \% uptake of gland}}{\text{mass of gland (grammes)}}$$

These workers aimed to give 7,000 rads for diffusely enlarged glands, 5,000 to 7,000 rads for small post-operative recurrences, and 8,000 rads or more for large and multinodular glands.

Follow-up Procedure

All patients were seen at monthly intervals at the endocrine clinic until they had become euthyroid. The assessment was initially made on clinical grounds but was confirmed by a basal metabolic rate (B.M.R.) estimation. The necessity for retreatment was considered three to four months after the initial dose. Dose prescription in the case of retreatment was based on the same principles as those for the first treatment. Doubtful cases were left for a further two months, and if by that time the presence of toxicity was still in doubt they were readmitted to hospital for further detailed study before a final decision was made. After patients became euthyroid they were seen at intervals of two to six months as the circumstances warranted. Cases suspected of hypothyroidism on clinical grounds were further investigated by estimations of serum cholesterol and of the B.M.R. and by electrocardiography. If the hypothyroidism was mild no replacement therapy was given, because it is known that transitory hypothyroidism may occur after ^{131}I therapy. If the hypothyroidism persisted for three to four months and became more marked, then L-thyroxine sodium was prescribed. Hypothyroidism was thought to have been produced by ^{131}I therapy only if treatment with thyroxine was necessary.

The minimum period of follow-up was one year and the maximum three and a half years. Cure was considered to have taken place if the patient was euthyroid at 12 to 18 months.

Biological Half-life of the Therapeutic Dose

The biological half-life of ^{131}I was measured in 13 patients of group 1 and 16 patients of group 2. This measurement was obtained as follows. An uncollimated scintillation counter with 1 in. (2.5 cm.) of lead filtration was used in conjunction with an Ekco autoscaler. On the second day after the therapeutic dose of ^{131}I had been administered the counter was set up 12 in. (30 cm.) above the isthmus of the thyroid gland and the radioactivity counted for 100 seconds. The neck was then shielded with 2 in. (5 cm.) of lead and a background count made in order to obtain the net radioactivity from the gland in counts per 100 seconds. This procedure was repeated at intervals until the gland radioactivity had fallen by one-half. After these values had been corrected for physical decay they were plotted against time, using semi-logarithmic paper, and the biological half-life was accepted as the time taken for the radioactivity to fall to half of its original value.

Results

Table I shows the clinical result of ^{131}I therapy in glands of different types.

Group 1 (28 cases).—Of the 28 patients in this group, only 8 (28.6%) became euthyroid with one dose of ^{131}I, though cure was achieved by 18 months in 24 (86%). Two patients developed hypothyroidism and there were two failures. The mean number of doses given to this group was 2.35.

Group 2 (45 cases).—The incidence of nodular and post-operative glands in this group was similar to that of group 1. The one-dose cure rate was 75.5% and the increase over the comparable figure for group 1 (28.6%) was statistically significant. Two cases of this group developed hypothyroidism and there were three failures. The mean number of doses given was 1.5.

Group 3 (21 cases).—Ten cases (47.5%) of this group became euthyroid with one dose. Two cases became hypothyroid, and there were no failures. The mean number of doses given was 1.9.

Group 4 (56 cases).—Thirty-three patients (59%) of this group became euthyroid with one dose, and this one-dose cure rate, while higher, was not significantly

*One rad = 100 ergs per gramme of tissue.

TABLE I.—*Results of ^{131}I Therapy*

Group	Type of Gland	No. of Cases	Euthyroid				Myxoedema			Still Toxic at 18 Months
			% of Total	Total	One Dose	2 or More Doses	Total	One Dose	2 or More Doses	
1	Diffuse (including not palpable)	19	68	17	7	10	0	0	0	2
	Nodular	6	21	4	0	4	2	1	1	0
	Post-thyroidectomy	3	11	3	1	2	0	0	0	0
	Total	28	100	24 (86%)	8 (28·6%)	16 (57·4%)	2	1	1	2
2	Diffuse (including not palpable)	28	62	27	25	2	1	1	0	0
	Nodular	11	25	8	5	3	1	1	0	2
	Post-thyroidectomy	6	13	5	4	1	0	0	0	1
	Total	45	100	40 (89%)	34 (75·5%)	6 (13·5%)	2	2	0	3
3	Diffuse (including not palpable)	14	67	12	6	6	2	2	0	0
	Nodular	7	33	7	4	3	0	0	0	0
	Post-thyroidectomy	0	—	0	0	0	0	0	0	0
	Total	21	100	19 (90·5%)	10 (47·5%)	9 (43%)	2	2	0	0
4	Diffuse (including not palpable)	29	52	28	19	9	1	0	1	0
	Nodular	21	37·5	17	10	7	3	0	3	1
	Post-thyroidectomy	6	10·5	6	4	2	0	0	0	0
	Total	56	100	51 (91·5%)	33 (59%)	18 (32·5%)	4	0	4	1

TABLE II.—*Biological Half-lives of Therapeutic Doses of ^{131}I*

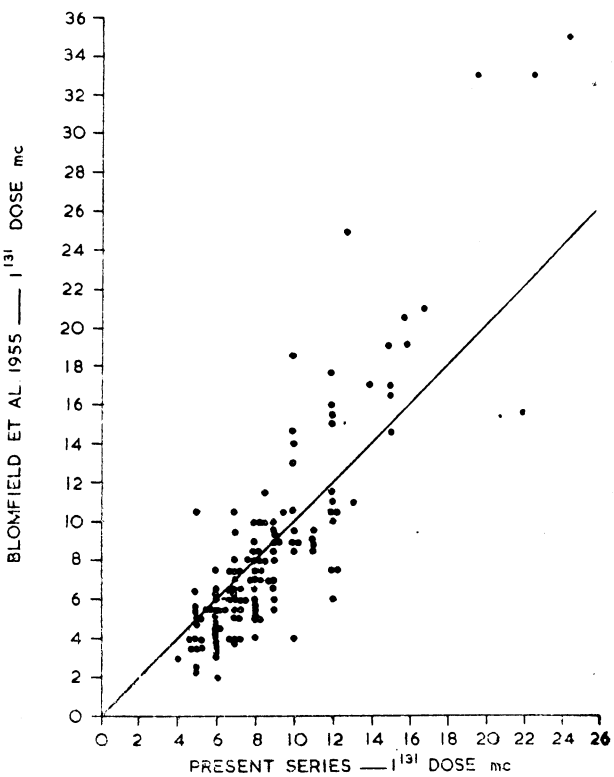
Cases Pretreated with Methylthiouracil (Days)		Cases with No Pretreatment (Days)	
9·4	9·0	17·8	12·4
13·2	11·3	17·0	10·0
13·0	14·8	20·0	15·6
8·0	11·0	4·7	4·0
5·0	20·0	7·0	7·0
8·5	6·0	14·4	23·0
14·0		7·4	15·2
		4·0	12·4
Mean = 11·0		Mean = 12·0	

different from that of group 3 (47.5%). Four patients of this group became hypothyroid, and there was one failure. The mean number of doses given was 1.6.

Biological Half-life of the Therapeutic Dose of ^{131}I.—The biological half-lives of ^{131}I of the 29 patients studied are shown in Table II. The mean biological half-life of the 13 patients of group 1 who had been pretreated with methylthiouracil was 11 days, and this was not significantly different from the comparable value of 12 days in the case of the 16 patients of group 2 who had received no pretreatment with an antithyroid drug.

Comparison of the Results of the Present Series with those of Blomfield et al. (1959)

In 101 cases of the present series not pretreated with methylthiouracil (groups 2 and 4) the one-dose cure rate was 68% and the incidence of hypothyroidism 6%. This was not significantly different from the one-dose cure rate (59%) and the incidence of hypothyroidism (12%) in 461 unpretreated cases reported by Blomfield *et al.* (1959). In the accompanying scattergram the doses used in the present series have been plotted against the doses which would have been used if the more elaborate method recommended by Blomfield *et al.* (1959) had been applied. It can be seen that in the lower-dose range there has been a tendency for the latter workers to give smaller doses, while in the higher-dose range larger doses have been given. This difference is not reflected in either the one-dose cure rates or the incidence of hypothyroidism in the two series.



Therapeutic doses of ^{131}I prescribed in the present series plotted against doses calculated from the formula of Blomfield *et al.* (1955). The oblique line has been drawn at 45 degrees to the ordinates.

Discussion

The results of radioactive iodine therapy in cases pretreated with methylthiouracil (group 1) showed a significantly lower one-dose cure rate than cases which had received no pretreatment (group 2). It can be seen from Table I that this finding cannot be accounted for by variations in gland types between the two groups. Furthermore, consistency of dosage prescription was obtained by the design of the observation which ensured that the same physician treated both groups during the same interval of time. Increasing the dose of ^{131}I in pretreated cases (group 3) raised the one-dose cure rate to that of an untreated control group (group 4). The findings could be explained if methylthiouracil pretreatment shortened the biological half-life of the therapy dose, but no significant difference was found between the mean biological half-lives of therapeutic doses of ^{131}I in a group of patients who had received the antithyroid drug before radioactive iodine therapy and in a group who had not. The difference between the pretreated and untreated groups could be due to a more patchy distribution of the therapeutic dose of radioactive iodine in the former, but there is no published evidence on this point.

The only other explanation which could account for the findings is that the methylthiouracil-treated gland is relatively radioresistant, and there is some experimental evidence to support this view. For instance, Dale (1947, 1952) and Dale *et al.* (1949) have demonstrated that thiourea protects carboxypeptidase, an enzyme in aqueous solution, against the effects of irradiation, and Limperos and Mosher (1950) have shown both *in vitro* and *in vivo* the same phenomenon in the case of nucleoproteins. The radioprotective effect of thiourea compounds has also been shown in bacteria (Forssberg, 1950) and in intact animals (Mole *et al.*, 1950; Lorenz *et al.*, 1952). Since there is some evidence that the diminished availability of intracellular oxygen produces radioresistance (Hollaender and Stapleton, 1953; Gray, 1954), the mechanism of the protective effect of methylthiouracil in the thyroid irradiated by ^{131}I may lie in the fact that it is a reducing agent. It is also of interest that other compounds containing sulphur or sulphydryl groups have a radioprotective action (Patt *et al.*, 1952; Rugh and Wang, 1953; Bacq, 1954; Gray, 1954). Rugh (1953) found that thiouracil gave protection to the thyroid cells of the Japanese fire salamander (*Triturus pyrrhogaster*) against irradiation by radioactive iodine for periods up to seven months following the cessation of administration of the drug. A similar effect in the human subject would explain why we observed relative radioresistance, though a week had elapsed between the last dose of the drug and the administration of ^{131}I.

This radioprotective action of methylthiouracil may explain the results obtained by Fraser *et al.* (1954). These workers pretreated patients receiving ^{131}I therapy with methylthiouracil and thyroxine. They subjected the thyroid to a much greater dose of radiation than Blomfield *et al.* (1955), but nevertheless recorded a smaller incidence of hypothyroidism.

The accurate determination of a single dose of radioactive iodine sufficient to produce cure of thyrotoxicosis presents the major practical difficulty in the application of this form of treatment. The majority of workers use techniques for estimating the therapeutic dose based on assumptions that the mass of the gland and the biological effect of ^{131}I can be accurately measured. It is generally recognized that the estimation of gland volume is inaccurate (Soley *et al.*, 1949 ; Loevinger, 1953 ; Kelly, 1954), and that the biological half-life of the therapeutic dose is difficult to predict from the turnover of a tracer dose (Skanse, 1948 ; Miller and Sheline, 1951 ; Freedberg *et al.*, 1952 ; Blomfield *et al.*, 1955). Though the uptake of the therapeutic dose of ^{131}I by the thyroid gland can be assessed with fair accuracy from the behaviour of a tracer dose (Keating *et al.*, 1949 ; Freedberg *et al.*, 1952), the distribution of the isotope in the gland has been shown to be very variable (Fitzgerald and Foote, 1949 ; Kelsey *et al.*, 1949), and especially so in nodular glands (Chapman and Maloof, 1955). The remaining factor which influences dose estimation is the sensitivity of the thyroid tissue to irradiation, and, though little is as yet known of the variability of this factor, there is evidence to suggest that considerable variation in gland radiosensitivity does occur (Myant and Pochin, 1955). Owing to these uncertainties it is not possible to estimate precisely the dose of radioactive iodine to give an optimum amount of irradiation.

Most published results in this field refer to groups of patients which include unspecified numbers of pretreated and untreated cases. Now that we have shown that pretreatment produces relative radioresistance, comparison with such series is impossible. Our results, however, in 101 untreated cases using a simple clinical dosage scheme compare favourably with those obtained in the unpretreated cases reported by Blomfield *et al.* (1959), who used an elaborate and quantitative predetermined dosage method. We agree with Macgregor's (1957) conclusion that precise methods of estimating the therapeutic dose of radioactive iodine offer no significant advantages.

It is of interest that when a simple clinical method of dose estimation is used the prescribing physician tends to be influenced in his decision by psychological factors. For instance, it can be seen (see Fig.) that the doses prescribed in the present investigation tended to be larger in the lower-dosage range and smaller in the higher-dosage range than those which would have been prescribed had the method recommended by Blomfield *et al.* (1955) been used. Thus when large doses have to be prescribed the physician using a purely clinical method tends to be unduly influenced by the dangers of potential hypothyroidism, whereas in the low-dose range he hopes to achieve cure with one dose and therefore is less inhibited. There is no statistical difference between the one-dose cure rates, probably because large doses are given relatively rarely and the percentage differences with larger doses are much less than with smaller ones. Halnan (1959) has pointed out that, because one needs to leave intact a constant mass of thyroid tissue and not to destroy a constant proportion of the gland, small glands will need a less-than-expected radiation dosage and large glands a higher dosage.

The present investigation has clearly confirmed that a simple technique without complicated measurements can be used provided simple rules are observed. This procedure achieves the maximum economy in both physician's and patient's time.

Summary

The one-dose cure rate in 28 patients who had been treated with methylthiouracil until the week before ^{131}I therapy (28.6%) was significantly lower than that of 45 patients who had had no previous drug therapy (75.5%). This difference could not be accounted for by differences in gland types or in the biological half-lives of the therapy doses of ^{131}I.

The dose of ^{131}I was increased by 25% in a further 21 patients pretreated with methylthiouracil, and the one-dose cure rate in this group (47.5%) was not significantly different from the one-dose cure rate in 56 patients who had received no pretreatment (59%).

It is concluded that pretreatment with methylthiouracil until one week before ^{131}I is given renders the gland relatively radioresistant.

A simple clinical method of dose prescription was used in this study, and the results obtained in 101 cases not pretreated with antithyroid drugs and observed for a minimum period of one year are as satisfactory as those reported in an investigation which aimed at delivering a predetermined amount of irradiation to the thyroid gland.

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