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RESPONSE TO TRIIODOTHYRONINE AS INDEX OF PERSISTENCE OF DISEASE IN THE THYROID REMNANT OF PATIENTS IN REMISSION FROM HYPERTHYROIDISM¹

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The present study was designed to determine the duration of activity of disease in the thyroid remnant of patients in sustained remission following treatment for hyperthyroidism. Failure of I-131 uptake to be decreased significantly by triiodothyronine administration was used as the criterion of persistence of disease. The recent observations that thyroid (1, 2) and triiodothyronine (3-5) do not decrease I-131 uptake when given to patients with overt disease indicate that the lack of response to these agents is fairly specific. Subjects without thyroid disease (1, 6-8) or patients with thyroid disorders other than hyperthyroidism show a sharp reduction in uptake; the one exception is found in nontoxic nodular goiter (4, 5) in which about 1 in 4 do not respond. The glands of such patients contain "hot," *i.e.*, highly active, nodules.

Rienhoff (9) and Roussy, Huguenin, and Welti (10) investigated the duration of thyrotoxicosis in the gland fragment remaining after surgery, using hyperplasia as a criterion. They studied the glands of six euthyroid patients coming to biopsy up to six years after operation, and found in all persistence of hyperplasia. Using the response to triiodothyronine as the criterion, the present investigation reveals that activity of disease within the gland remnant may persist for more than 20 years after remission was induced by one of the modalities of treatment; or may subside within a few months of the onset of remission. Abnormal responses appear to predominate in the first five years after I-131 therapy whereas the number of normal responses in the same time period following surgery equals or is greater than the abnormal ones. Normal responses predominate after the five-year interval in both groups.

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METHODS

All patients tested had had documented toxic diffuse or toxic nodular goiter and had been in remission for various lengths of time before the study was made. The duration of euthyroidism prior to testing with triiodothyronine is recorded in Table I.

Most of the patients were originally seen, treated, and followed subsequently, in the Thyroid Clinic of the Presbyterian Hospital in New York. The usual modalities of treatment are represented in the series. Just prior to testing with triiodothyronine, all patients were examined by the writer and were sent to the laboratory for determinations of basal metabolic rate, fasting serum cholesterol and 24-hour I-131 uptake by standard methods. The serum precipitable iodine level was also measured by the original Barker method (11) when there was disagreement among the other tests. Only those patients are included in the series who seemed unquestionably euthyroid and who had been so, as best as could be determined, for the interval stated in the table.

Following the above appraisal, the patients were tested with triiodothyronine according to the method described elsewhere (4). After determination of the 24-hour I-131 uptake, each patient was given 1-sodium triiodothyronine by mouth, 75 μ gm. daily for 8 days. On the eighth day, a count was made over the thyroid, to account for radioactivity remaining from the preceding test. A second test dose of I-131 was then administered and uptake measured 24 hours later. Test doses of 15 μ c I-131 each were employed. A bismuth cathode Geiger tube was used for counting over the thyroid region with the counter placed 15 cm. from the skin and able to see an area about 10 \times 10 cm. Counting time was about 10 minutes (2000 counts) to provide a counting accuracy of about 3 per cent with the background count subtracted.

Throughout, a response was termed "normal" when the final I-131 uptake value after triiodothyronine administration was less than 20 per cent, or was not more than 60 per cent of the initial value when the initial uptake was already low. There were virtually no values in this group with a final value as much as 50 per cent of the initial value. The response was termed "abnormal" if the final value was 30 per cent or more, or was 60 per cent or more of the initial value when the initial uptake was low.

TABLE I

Table showing duration of euthyroidism, type of treatment, and distribution of responses to triiodothyronine in patients in remission from hyperthyroidism following treatment

Therapy	Patient category	Duration of euthyroidism (Years)													Total
		<1	1	2	3	4	5	6	7	8	9	10-14	15-19	20-	
I-131	Normal * (No. of patients)	1	2	1	5	1	1	4	2	1					18
	Abnormal * (No. of patients)	11	9	10	4	8	4	0	1	1					48
Operation	Normal (No. of patients)	1	6	1	1	1	1	1	1	1	0	1	2	0	17
	Abnormal (No. of patients)	0	2	2	0	1	0	0	0	0	1	2	0	2	10
Antithyroid	Normal (No. of patients)	0	0	1	0	0	0	1	2	0	1	0	0	0	5
	Abnormal (No. of patients)	1	0	1	0	0	0	0	0	1	0	1	0	0	4
Miscellaneous	Normal (No. of patients)	0	0	0	0	0	1†	0	0	0	0	0	0	1‡	2
	Abnormal (No. of patients)	0	1‡	0	0	0	0	0	0	0	0	0	0	0	1
														Total	105

* For definition, see text under "methods."

† Remission following radiotherapy.

‡ Spontaneous remission.

RESULTS

The results are summarized in Table I. There were 105 patients in four therapeutic categories: 1) I-131 treatment—66 patients; 2) Subtotal thyroidectomy—27 patients; 3) Chronic antithyroid drug therapy (mostly maintained for a year or more before discontinuance)—9 patients; 4) Miscellaneous—1 patient treated by roentgen therapy and 2 patients entering remission spontaneously. A few patients originally with toxic nodular goiter were studied and the results combined with those

TABLE II

Table showing mean 24-hour I-131 uptake values before and after triiodothyronine administration in patients in remission from hyperthyroidism following treatment by I-131 or operation

Therapy	Duration of remission	Response					
		Normal			Abnormal		
		Number of patients	Average 24 hr. uptake		Number of patients	Average 24 hr. uptake	
Years		Initial	Final		Initial	Final	
I-131	0-5	11	28	11	46	34	34
	6-	7	27	10	2	23	18
Operation	0-5	11	25	12	5	38	37
	6-	6	28	8	5	36	38

of the toxic diffuse group because no special trend was observed.

A. I-131 treatment

There were 66 patients who had been given I-131 from several months to 8 years before testing (Table I). Following triiodothyronine administration, 17 patients showed a normal response (Tables I, II, III). The earliest return to normal was at 4 months after treatment, whereas lack of response, *i.e.*, evidence of activity of disease, was still present almost 9 years after therapy. Prior to 5 years, the ratio of abnormal to normal responses was approximately 5 to 1; subsequently 1 to 3. Statistical analysis of this difference in ratios reveals that $\chi^2 = 10.1$ which is significant at better than the 0.1 per cent level. Also, the mean of the time after I-131 therapy for those with an abnormal response is 3.2 years whereas it is 4.3 years for those with a normal response. This is significant at better than the 1 per cent level.

B. Subtotal thyroidectomy

There were 27 patients in the operative series. Seventeen of these showed a normal response and

TABLE III

Table showing distribution of I-131 uptake values before and following administration of triiodothyronine

% Uptake	Therapy			
	I-131 Number of uptake values		Surgery Number of uptake values	
	Initial	Final	Initial	Final
<i>Normal response group</i>				
0-9	0	7	0	8
10-19	2	9	3	9
20-29	10	2	8	0
30-39	4	0	5	0
40-49	2	0	1	0
50-59	0	0	0	0
60-69	0	0	0	0
70-	0	0	0	0
Total	18	18	17	17
<i>Abnormal response group</i>				
0-9	0	0	0	0
10-19	4	6	2	1
20-29	11	17	1	2
30-39	15	11	3	2
40-49	5	7	0	2
50-59	3	5	2	2
60-69	2	1	1	1
70-	0	1	0	0
Total	40*	48	9*	10

* Values excluded were determined more than two months prior to the administration of triiodothyronine.

10 an abnormal one. A normal response was noted within 1 year of operation, and abnormal responses were elicited more than 20 years after treatment (Tables I and III). Normal responses tended to preponderate in the first 5 years after operation, the ratio being about 2 normal to 1 abnormal response and 6 to 5 after 5 years (Table II). The difference in the ratio in the first 5 years from that found after I-131 therapy has a significance better than the 0.1 per cent level with $\chi^2 = 11.7$. The number of patients is too small to be sure of significance in the difference in ratios before and after 5 years following surgery.

C. Chronic antithyroid drug therapy

The number of patients in remission following cessation of chronic antithyroid drug therapy is small (Table I). One patient showed no response to triiodothyronine as late as 12 years after remission and on the other hand, a normal response was noted at the earliest time tested, 2 years after remission.

D. Miscellaneous

One patient in this group received external radiation therapy with x-rays. This patient was tested 5 years after remission and exhibited a normal response to triiodothyronine (Table I). There were two patients in spontaneous remission from hyperthyroidism. One showed an abnormal response 1 year after becoming euthyroid, and the other tested 22 years after, had a normal response (Table I).

DISCUSSION

In hyperthyroidism, I-131 uptake by the thyroid is not decreased significantly by the administration of triiodothyronine. This lack of response has been seen otherwise only in nontoxic nodular goiter with "hot" nodules within the gland (4, 5). Lack of response in toxic goiter presumably therefore is indicative of activity of disease. As was noted in the earlier studies, in 10 of 13 patients given thyroxine (12) and 3 of 17 patients given thyroid (1) as well as with this test (4) and documented here, a return to normal responsiveness may occur after sustained remission of hyperthyroidism has been induced by appropriate therapy; this presumably represents subsidence of the disease. Continuance of an abnormal response after remission therefore presumably implies persistence of disease within the gland remnant, despite the euthyroidism. It is unlikely that an abnormally rapid disposal of triiodothyronine, demonstrated in patients with hyperthyroidism and in remission from the disease (13), could account for lack of response of uptake in the present series in view of the daily doses and size of doses which were used and the prolonged duration of treatment, 8 days.

The finding that activity of hyperthyroidism within the thyrotoxic remnant may persist for long periods of time or may subside at varying intervals of the treatment corresponds with the information from earlier histological studies (9, 10). This work revealed by biopsy that hyperplasia had persisted in the thyrotoxic remnant of patients as late as 6 years after remission from successful surgery. The series included only six patients. In a more recent study of seven patients dying of various diseases somewhat later after the onset of remission, histopathological evidence

of persistence of disease was noted as late as 7 $\frac{3}{4}$ years, possibly 13 years, after surgery (14). However, the use of hyperplasia as the criterion for persistent activity of disease is open to the criticism that the increased cellular activity could conceivably be a compensatory response to removal of most of the gland.

In the present data, an abnormal response to triiodothyronine is seen for the first 5 years after I-131 in the majority of patients, but thereafter the response of the majority is normal. This implies that there is active disease within the thyrotoxic remnant which was not eliminated by therapy or the establishment of euthyroidism, but which ultimately does subside spontaneously. However, a distinct and highly significant difference from this group is seen when the response to triiodothyronine of the patients treated surgically is examined. Here the majority exhibit a normal response as early as 1 to 2 years after operation as stated above. The difference in time is significant to better than the 0.1 per cent level, although the series is small.

The explanation for the fact that surgical patients seem to revert to normal earlier than I-131 treated patients is not clear. After I-131 therapy, presumably only those cells resistant to radiation effect survive, whereas after surgery the cells which remain possess the same properties as those removed. Subsidence of the disease in the remnant could conceivably be influenced by this factor of selection, the radio-resistant cells being slower to recover. However, it is of interest that an abnormal response to triiodothyronine may persist in antithyroid drug treated patients and following spontaneous as well as induced remission. Another factor of selection lies in the fact that older patients or patients with recurrent hyperthyroidism are usually selected for I-131 therapy and younger ones for surgery. Whether these factors could cause the disparity in results between the 2 groups is subject for speculation.

Besides the abnormality in response to triiodothyronine, there is an abnormal response to thyrotropin in active hyperthyroidism (15), and this may persist after sustained remission has been induced (1). Actually there is a dichotomy of response to thyrotropin: I-131 uptake is unaffected but release of secretion is accelerated as evidenced by an increase in level of serum precipitable io-

dine (1, 15). The lack of response to thyrotropin of the uptake in patients in remission following treatment for hyperthyroidism has been recently confirmed in another laboratory although no response of the serum precipitable iodine occurred (16). However, a few of the post-treatment patients of the original study and in this later series did develop an increased uptake following thyrotropin injection and an increase in serum precipitable iodine. This normal responsiveness suggests that they might also have exhibited normal responsiveness to triiodothyronine if they had been so tested. This supposition requires documentation.

Uptake of I-131 by the thyroid, also, is not increased by thyrotropin in euthyroid patients with early eye signs of Graves' disease although the serum precipitable iodine level becomes elevated (17). Since the uptake of these patients is well within the normal range, the discrepancy between effects on uptake and release has been taken as added evidence that the derangement is in the thyroid cells or is mediated by unknown mechanisms rather than that a hyperfunctional pituitary because of its increased thyrotropin release has caused the Graves' disease (15). The observation that the activity of disease within the thyroid remnant after treatment for hyperthyroidism limited to the thyroid gland may subside earlier after one modality than after another again suggests that the disorder within the gland is not mediated through the pituitary.

Finally, it appears reasonable to postulate that patients who maintain active disease in the thyroid remnant are the ones who are more apt to develop recurrent hyperthyroidism than those in whom the disease has subsided. It is clear that the triiodothyronine test is positive at the time of recurrence of hyperthyroidism (4). If this assumption be true, the use of triiodothyronine would have prognostic, as well as diagnostic, value. Conversely, it must be remembered in using the test that the patient suspected of recurrent hyperthyroidism may exhibit an abnormal response even though euthyroid.

SUMMARY

1. Duration of activity of disease in the thyroid remnant has been studied in patients in sustained

remission from hyperthyroidism subsequent to treatment by the usual modalities. An abnormal response of I-131 uptake by the thyroid following the administration of triiodothyronine has been taken to indicate such activity.

2. Evidence of active disease within the gland was found at well beyond 20 years after onset of remission and subsidence of disease occurred as early as 4 months after therapy as shown by a return to normal of the I-131 uptake response to triiodothyronine.

3. The majority of patients tested showed evidence of activity of disease within the gland for the first 5 years after I-131 therapy and of subsidence of disease thereafter. By contrast, in the majority of a small group of patients after surgery, the activity of the disease subsided within 1 to 2 years. A few patients treated previously by chronic antithyroid drug therapy, one patient treated by roentgen therapy and two patients in spontaneous remission were also studied.

4. The possibility that the response to triiodothyronine may be abnormal despite euthyroidism in patients previously treated for hyperthyroidism must be taken into account when the triiodothyronine test is used in the diagnosis of recurrent hyperthyroidism.

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