A NEW AND SIMPLE TEST FOR HYPERTHYROIDISM EMPLOYING L-TRIIODOTHYRONINE AND THE TWENTY-FOUR-HOUR I-131 UPTAKE METHOD*

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THE administration of thyroid, thyroxine or triiodothyronine causes a sharp reduction in I-131 uptake by the thyroid in euthyroid subjects[1-4] but little if any change in Graves' disease.[4-6] This distinction is so clear-cut that an investigation was undertaken to establish whether the reaction would be as useful diagnostically as these results implied. Since thyroid contains iodides and several organic iodinated compounds which might induce false positive results, and since also the effects of thyroid and of thyroxine are protracted after treatment is discontinued, crystalline-triiodothyronine was chosen as the test agent. The material is available in pure form and has a more rapid half-life within the body than thyroxine.[7] While this study was being pursued, Greer[8] independently was investigating the use of thyroid for the same purpose and obtained similar results.

METHODS

Patients with a variety of clinical disorders were tested. Pills containing 35 μg. of triiodothyronine were employed at first but the strength was reduced during the experiment to 25 μg.† Thus doses varied during the experiment from 70 to 75 and 140 to 150 μg. given daily for eight days by mouth. Dosage was begun after an initial twenty-four hour I-131 thyroidal uptake was determined, using a 15 μc. dose of I-131; measurements were made directly over the thyroid by means of a bismuth cathode Geiger tube. On the eighth day of triiodothyronine treat-

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TABLE I—TABLE SHOWING DISTRIBUTION OF INITIAL TWENTY-FOUR HOUR I-131 UPTAKE VALUES

Patient Category	*No. Patients*	*Initial 24 hour I-131 uptake %* 39 *or less*	40-54	55 *or more*
Euthyroid controls	48	30	13	5
Nontoxic goiter				
diffuse	16	8	7	1
nodular	19	14	4	1
Untreated toxic goiter	48	2	13	33
Treated toxic goiter, euthyroid	12	9	2	1
Early eye signs of Graves' disease, euthyroid	10	6	3	1
Total	153	69	42	42

ment, residual radioactivity in the thyroid was measured and 15 μc. I-131 administered for the second time. The next day, uptake was determined, allowance being made for the I-131 remaining from the initial test. The lapse of eight days following the start of treatment was suggested by early studies with small and large doses of triiodothyronine given daily with uptake measured at varying intervals from the start of treatment. Six patients were given a single 500 μg. dose of triiodothyronine and the uptake followed daily. Uptake began to decrease after as little as forty-eight hours but did not reach a minimum uniformly, requiring between three and eight days for the complete response to be achieved.

All patients were examined by one of us (S.C.W.) and the diagnosis established on clinical and laboratory grounds other than the response to triiodothyronine subsequently obtained.

RESULTS

A total of 138 patients were given triiodothyronine diagnostically. The various patient categories are listed in the tables. All patients used as control subjects and without demonstrable thyroid disease are grouped together under the heading "euthyroid controls." This group is heavily weighted with high initial uptake values because of the effort to collect

TABLE II—SUMMARY TABLE SHOWING THE EFFECT OF TRIIODOTHYRONINE UPON TWENTY-FOUR HOUR I-131 UPTAKE. THE SMALLER NUMBER AFTER THE MEAN GIVES THE STANDARD ERROR OF THE MEAN.

Patient Category	*No. Patients*	*Daily Dose Triiodothyronine μg.*	*Average 24 Hour I-131 Uptake* *Before*	*After*
Euthyroid controls	41	75	37 — 2.2	12[1]— 1.4
	7	35	30	10
Nontoxic goiter				
diffuse	16	75	40	9[2]
nodular	13	75	34	15[3]
	8	150	31	14
Untreated toxic goiter	20	75	56 — 3.4	62[4]— 3.4
	28	150	63 — 9.0	63[4]—11.1
Treated toxic goiter, euthyroid	12	75	34	15[5]
Early eye signs of Graves' disease, euthyroid	10	75	34	32[6]

Footnotes—1. One value 36%, falling to 1% with 150 μg. daily.
2. One value 26%.
3. Three values more than 20% (24%, 27%, 30%).
4. No value less than 35%.
5. Two patients showed no response and were subsequently found to have active disease.
6. Two patients included received thyroid daily 0/12 Gm. and 0/18 Gm. respectively for 8 days.

TABLE III—TABLE SHOWING PER CENT DECREASE IN I-131 UPTAKE (INITIAL UPTAKE-FINAL UPTAKE) RESULTING FROM TRIIODOTHYRONINE ADMINISTRATION

Patient Category	*Change in uptake (%)* ±0 *or increase*	—1 —9	—10 —19	—20 —29	—30 *or less*
Euthyroid	1	2	8	16	14
Nontoxic goiter					
diffuse	0	0	3	5	8
nodular	1	6	7	2	5
Untreated toxic goiter	33	11	3	0	1
Treated toxic goiter	0	3	2	6	1

such patients for study. The nontoxic goiter group has been divided into diffuse and nodular but this has not been done for the toxic goiter group because no difference between the responses of toxic diffuse and toxic nodular goiter was evident.

Eighteen of forty-eight euthyroid control patients (37 per cent) had initial uptakes of 40 per cent or more; fifteen of forty-eight hyperthyroid patients (31 per cent) had initial uptakes less than 54 per cent (Table I). The percentages of overlap are somewhat less for the nontoxic nodular goiter group and somewhat more for the nontoxic diffuse group but the number of patients is small.

In all groups except toxic goiter and the euthyroid patients with the early signs of Graves' diseases, the administration of 75 μg. triiodothyronine daily for eight days resulted in a uniform decrease in I-131 uptake to 20 per cent or less (Tables II and III). There was one exception in the euthyroid control group in which the uptake increased from 24 per cent to 36 per cent with 75 μg. triiodothyronine daily, but with a dosage of 150 μg. for eight days, the uptake was depressed to 1 per cent. A daily dose of 35 μg. was given to seven euthyroid control patients with all but one patient having an uptake less than 20 per cent on the eighth day of treatment. In the nontoxic diffuse goiter group, one of the sixteen patients had an uptake which failed to decrease to less than 20 per cent, although a decrease had occurred from 44 per cent to 26 per cent; uptake was not further reduced by daily doses of 150 μg. triiodothyronine. Five of the twenty-one patients in the group with nontoxic nodular goiter, three with single nodules in the gland and two with multiple nodules had uptakes after triiodothyronine administration between 20 per cent and 30 per cent, the rest being less than 20 per cent. Their initial twenty-four hour I-131 uptakes within the normal range did not suggest hyperthyroidism. Radioautographs of the specimens obtained at operation upon three of these patients revealed significant uptake by the nodules as well as by the parenchyma of the gland.

In the toxic goiter group, no I-131 uptake was less than 35 per cent following triiodothyronine doses of either 75 or 150 μg. A group of ten euthyroid patients with early eye signs of Graves' disease was observed (Fig. 1) in whom uptake failed to respond to the administration of triiodothyronine, even though the initial uptakes were within the normal range, exceeding 45 per cent in only two instances. This was

Fig. 1A

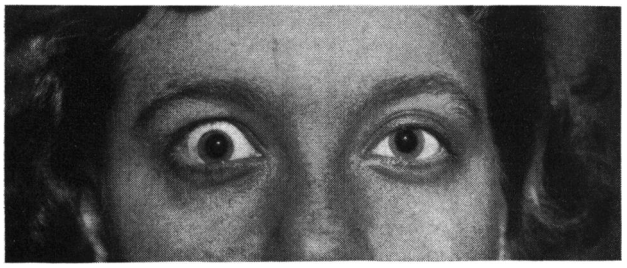

Fig. 1B

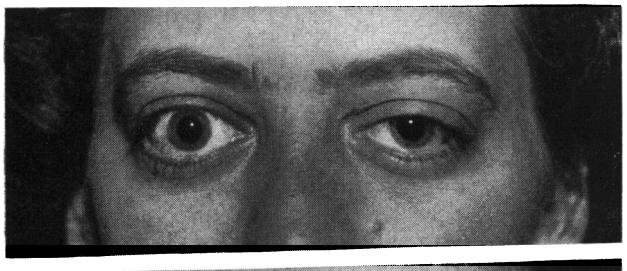

Fig. 2

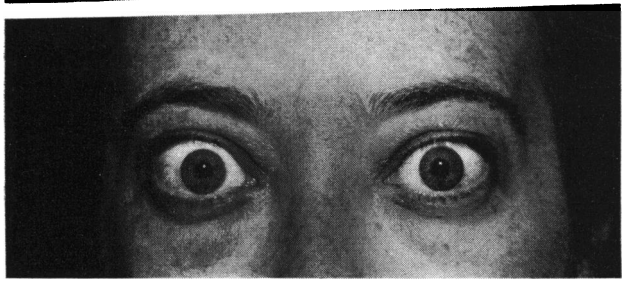

Fig. 1—A. and B. Euthyroid patients D.S. and M.E. with early eye signs of Graves' disease. The I-131 uptake did not decrease upon triiodothyronine administration.

Fig. 2—Patient E.R. with acute myeloblastic leukemia involving the orbits. I-131 uptake fell in response to triiodothyronine dosage.

in contrast to twelve patients with residual eye signs of Graves' disease after remission from the hyperthyroidism had been induced previously by definitive therapy. A sharp drop in I-131 uptake was noted in all but two of the latter upon triiodothyronine administration, and these two patients shortly thereafter became more obviously ill of recurrent disease. In three additional patients with eye signs which created confusion diagnostically with those of Graves' disease but subsequently proven to have other diseases, a normal response to triiodothyronine was observed and uptake dropped to less than 20 per cent. Two of these had pseudotumor of the orbit and one, acute myeloblastic leukemia (Fig. 2).

The extent of decrease in I-131 uptake following triiodothyronine dosage is of interest (Table III). Forty-four of the forty-eight toxic goiter patients responded with a decrease of less than 10 per cent whereas thirty-eight of the forty-one euthyroid control subjects had decreases in excess of 10 per cent and in fact thirty of the forty-one a decrease exceeding 20 per cent.

Discussion and Conclusions

The present study indicates that the response of the twenty-four hour I-131 uptake by the thyroid to the administration of triiodothyronine in 75 to 150 μg. doses offers a clean-cut separation between toxic goiter and euthyroid subjects without thyroid disease. Euthyroid subjects with one exception had an uptake of 20 per cent or less following treatment with 75 μg. daily whereas in no instance was the final uptake less than 35 per cent in toxic goiter even when 150 μg. daily were given. The one exception among the euthyroid patients responded with a 1 per cent uptake when 150 μg. were given.

Patients with active hyperthyroidism can also be differentiated with this technique from patients with inactive disease in whom a sustained remission had been induced by definitive therapy; and also from patients with nontoxic diffuse and nontoxic nodular goiter. The test is simple and requires only the performance of two I-131 uptake tests, one before, and a second after triiodothyronine has been taken by mouth for a week. No special equipment is required beyond that needed for the twenty-four hour I-131 uptake method alone and the test is useful for the ambulatory patient.

A dose of at least 75 μg. daily is suggested to insure uniformity of response by the euthyroid patients. Although Starr[3] observed a decrease in uptake with as little as 8 μg. daily in healthy subjects, 35 μg. given daily in the present series resulted in one failure in seven patients tested, and one patient was seen who did not react to 75 μg. although responding vigorously to twice that amount. No side reactions have been observed from the use of triiodothyronine at the 75 μg. dose level which could not have been attributed equally to anxiety. At the 150 μg. level, euthyroid patients generally complain of mild increase in tension and nervousness; infrequently, epigastric fullness, increased palpitation, nausea and vomiting, paroxysmal hacking cough, or headache may occur. One patient only could not complete the test because of nausea,

vomiting and palpitation on the larger dose but her physician stated this occurred with all medication. No definite evidence of increase in the toxicity of existing hyperthyroidism has been observed. Symptoms generally subside within a day or two of stopping the drug.

About a third of values for the initial twenty-four hour uptake in the euthyroid patients of the present series exceeded 40 per cent, some extending beyond 50 per cent (Table I). Values in this range were not conclusive diagnostically because about a third of initial values in untreated hyperthyroidism were less than 55 per cent extending rarely below 40 per cent (Table I). In a larger series from the routine laboratory of the hospital in which the factor of selection weighted the percentages less, this figure was somewhat less, 16.4 per cent of patients having indeterminate uptakes. It is in clarifying the diagnosis of this group of patients that the use of triiodothyronine serves its largest purpose.

Patients with eye signs suggestive of Graves' disease should be tested with triiodothyronine regardless of the initial uptake value. The identification of a group of euthyroid patients with recent onset of typical early eye signs of Graves' disease was made possible by their failure to respond to triiodothyronine. The failure of the uptake to be suppressed by triiodothyronine administration to this group suggests that these patients have active Graves' disease despite their euthyroidism: the response conforms to that of patients with active Graves' disease.

The response to triiodothyronine in active Graves' disease is in sharp contrast to that of patients brought into remission from the disease by successful treatment and tested after having been well for one to fifteen years. In these latter patients, a normal response to triiodothyronine was noted in all but two, and these two shortly developed overt hyperthyroidism. It would thus appear that the test may be useful in establishing activity of the eye complications of the disease, as well as of the hyperthyroidism. One euthyroid patient was tested twice, during the period of active ophthalmopathy after subtotal thyroidectomy, and after the onset of spontaneous remission. Uptake was unchanged by triiodothyronine treatment in the active phase, 22 per cent initially and 20 per cent after; but was decreased definitely in the phase of remission, 19 per cent initially and 9 per cent after. By the same token, patients with eye signs simulating those of hyperthyroidism but due to other diseases, can be distinguished from Graves' disease. Three such patients

were tested and showed a normal decrease in I-131 uptake following triiodothyronine administration.

About half of the initial twenty-four hour I-131 uptake values in patients with nontoxic diffuse goiter in the present series were 40 per cent or more. The responses when triiodothyronine was given were like those of the control subjects without thyroid disease. One patient did not respond well but the final value was 26 per cent which was less than the lowest value of 35 per cent occurring in toxic goiter in response to the agent.

The patients with nontoxic nodular goiter in whom uptake failed to decrease upon triiodothyronine administration have not constituted a difficult diagnostic problem since initial and final uptakes were within the normal range. Radioautographs of surgical specimens of the thyroids of three of these five patients were made at a later date and revealed the nodules to have been about as functional as the surrounding normal tissue. This finding is being pursued in order to determine if the thyroid parenchyma, the nodules, or neither, become inactive functionally in response to triiodothyronine.

Summary

1. Triiodothyronine, 75 or 150 micrograms daily by mouth for eight days, caused a sharp decrease in the twenty-four hour I-131 uptake in forty-eight euthyroid patients without thyroid disease so that no value exceeded 20 per cent. In contrast, no value under 35 per cent was obtained in patients with toxic goiter following triiodothyronine administration. Side effects occurred in euthyroid patients only, with a dosage of 150 μg. and were relatively minor.

2. About a third of the euthyroid patients in this series had initial twenty-four hour I-131 uptake values in excess of 40 per cent, and a third of the hyperthyroid patients had uptakes less than 55 per cent. Triiodothyronine was virtually specific in clarifying the diagnosis in this group with overlapping values.

3. Triiodothyronine was valuable in establishing the activity of the eye complications of Graves' disease. Euthyroid patients with the early eye signs of Graves' disease and patients with overt hyperthyroidism showed an abnormal response to triiodothyronine but patients in sustained remission reacted normally.

4. Patients with nontoxic diffuse goiter responded like normal

subjects to the administration of triiodothyronine, whereas five of the twenty-one patients studied with nontoxic nodular goiter had no response to triiodothyronine administration, even though the initial uptake values were within the normal range. Radioautographs of three of these glands revealed the nodules to be functionally active.

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