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Thyroid Reserve in Euthyroid Patients After Ablative Therapy for Diffuse Toxic Goiter

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Thyroid reserve was measured in 41 patients who were euthyroid 5 to 15 years after therapy for diffuse toxic goiter. Twenty-one of them had been treated by ^{131}I, 20 by surgery and 10 were normal controls. All had a PBI (protein bound iodine) and 3-hour thyroidal ^{131}I uptake. The same parameters of function were measured again 24 hours after they were given 10 units of thyroid stimulating hormone (TSH) intramuscularly. Only two patients in each treatment group responded with normal elevation of both the PBI and ^{131}I uptake. In 52% of the ^{131}I-treated patients and in 55% of those surgically treated there was no significant increase in either PBI or thyroidal iodine uptake. These results suggest that current efforts to reduce the early post ^{131}I incidence of hypothyroidism may result in a long-term reduction of this complication as well and make this group comparable to those treated surgically. It is certain, however, that no patient receiving either therapy should be dismissed from continuing medical followup.

There are few documented reports of untreated patients with diffuse toxic goiter, but it has been known since 1888 that the natural course of Graves' disease for some patients leads to hypothyroidism.[1-2] Because this has become more common as a result of ablative therapy for diffuse toxic goiter, the prevention of post-therapy hypothyroidism is a major problem. Recent studies have demonstrated an increasing incidence of hypothyroidism with each subsequent year after therapy. A somewhat lower incidence per year has been reported for patients who have undergone subtotal thyroidectomy[3-9] than for those treated with ^{131}I.

Months or years following the surgical or radioiodine therapy of Graves' disease the abnormal stimulator of the thyroid gland may disappear and the normal hypothalamic pituitary thyroid relationships return. Theoretically it is then possible to detect the functional capacity of the thyroid remnant which is in excess of that necessary for maintaining the euthyroid state. The concept and significance of "thyroid reserve" was first described by Jefferies et al.[10] He described the response of

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both the protein bound iodine (PBI) and the radioiodine uptake to a standard dose of thyroid stimulating hormone (TSH) and noted that either index of response could be abnormally low in a euthyroid patient. The present study was designed to determine the degree of such responses in patients who were euthyroid at least five years after therapy for diffuse toxic goiter.

All euthyroid patients available for restudy were included. No attempt was made to compare the incidence of hypothyroidism occurring after the two modes of therapy, since our interest was in determining the behavior of the thyroid remnant surviving either treatment.

Methods

Thyroid reserve as described by Jefferies[10] was measured in 41 euthyroid subjects, 5 to 15 years after therapy for hyperthyroidism, and in 10 "controls." Of the first group, 21 had received between 2.5 and 30.0 mc of ^{131}I and 20 had undergone subtotal thyroidectomy as definitive therapy for their diffuse toxic goiter.

The diagnosis of Graves' disease prior to therapy was initially established on a clinical basis and was supported by determination of the basal metabolic rate (BMR), PBI or 24-hour ^{131}I uptake. Excluded from this study were all patients with hyperthyroidism caused by a single hyperfunctioning nodule or a long standing multinodular goiter, and those who had received both surgery and ^{131}I therapy.

The control group (data shown in Table I) was made up of volunteers judged to be euthyroid by clinical examination. They had normal PBI responses, no familial history of thyroid disease and no thyroid enlargement. Each was examined by one of the authors and the PBI was obtained to confirm the clinical impression.

Each was given 10 μc of ^{131}I by mouth and the uptake was measured three hours later. Ten units of TSH (Thytropar, Armour) were then given by intramuscular injection. The ^{131}I uptake was measured 24 hours prior to the administration of a second 10 μc for determination of the stimulated three-hour uptake. Blood for a PBI was drawn at the end of the second three-hour uptake. Thus both an index of hormone release[12-14] and of hormonal synthesis[15] after TSH were measured. The normal PBI in our laboratory ranges between 4.0 and 8.0 μg%. The normal three-hour uptake is between 5% and 15%.

Results

An increase of 1 μg% of PBI and a 5% result in the three-hour uptake represented a significant response, as measured in our controls and by the studies of Jefferies.[10] All controls (Table I) had at least that great a response, with a range of increase from 1.1 to 3.3 μg% of PBI and from 8.9% to 15.0% in uptake.

Table II represents the data from the ^{131}I-treated patients and Table III contains the results in the surgically treated patients. Average age was 38.9 years for surgical patients and 52.4 years for those treated with the ^{131}I. The time elapsed since therapy averaged nine years for the surgical group and 9.3 years for the irradiated group. The higher-than-normal PBI in surgical patient #18 was related to increased thyroxine binding globulin from an oral contraceptive. It is, therefore, not

TABLE I

CONTROL

			3 Hour Uptake (%)			Serum PBI (mcg %)		
No.	Age	Sex	Before TSH	After TSH	Change	Before TSH	After TSH	Change
1	39	F	6.8	20.6	13.8	4.6	7.0	2.4
2	54	F	7.9	19.1	11.2	4.7	7.7	3.0
3	49	F	17.6	32.6	15.0	5.8	8.8	3.0
4	41	M	9.1	18.5	9.4	4.1	5.5	1.4
5	36	F	7.1	19.0	11.9	4.1	6.0	1.9
6	66	M	3.4	17.5	14.1	4.7	6.0	1.3
7	35	F	12.3	22.2	9.9	4.5	7.8	3.3
8	40	F	11.3	21.6	10.3	5.4	6.9	1.5
9	20	F	12.9	23.9	11.0	5.1	6.4	1.3
10	19	F	8.0	16.9	8.9	4.7	5.8	1.1
					10*			10*

* Number of patients with a significant increase

a true measurement of thyroid function.[16]

A significant increase in both parameters of thyroid function after TSH appeared in only two patients out of the 21 tested in the ^{131}I treated group. In 11 patients (52%), neither the PBI nor the uptake responded significantly. The group of eight patients in which only the uptake was significantly elevated is believed to represent those with additional secretory capacity but with low hormone storage.

In the group of 20 patients who underwent subtotal thyroidectomy only two responded normally. Again, 11 (55%) exhibited no significant response in either measurement. Only four of the surgically treated patients responded to TSH with increase of the uptake, while this result occurred in 10 of the ^{131}I-treated group. On the other hand, only two of the irradiated group responded with elevated PBI, while in the surgically treated, seven patients were found responsive. These differences are of questionable statistical difference.

In both groups, some patients exhibited a greater drop in the iodine uptake after TSH stimulation than could be expected from the inherent error of the measurement. This observation may be explained by a drop in the background count during the second three-hour uptake. The accelerated turnover of ^{131}I in the thyroid remnant after stimulation by TSH could produce this variation. The PBI also decreased in several cases in both groups, but values were within the error of reproducibility of the method.

Discussion

The use of thyrotropin in the study of the pathophysiology of the thyroid gland was suggested over 30 years ago.

TABLE II

131-I Treated

No.	Age When Studied	Sex	Years Since Therapy	3 Hour Uptake (%) Before TSH	After TSH	Change	Serum PBI (mcg %) Before TSH	After TSH	Change
1	57	M	5.6	5.7	46.0	40.3	4.2	5.5	1.3
2	49	F	9.3	9.7	7.4	-2.3	3.0	3.5	.5
3	53	M	10.2	13.7	11.0	-2.7	3.9	4.1	.2
4	47	F	11.2	10.5	17.8	7.5	4.3	4.2	-.1
5	62	M	9.7	7.9	12.5	4.6	4.4	4.8	.4
6	52	F	9.0	13.7	14.0	.3	5.5	5.5	0
7	55	F	9.1	8.0	10.6	2.6	4.0	3.9	-.1
8	42	F	9.0	12.0	20.0	8.0	4.4	4.0	-.4
9	46	M	9.7	10.7	24.9	14.2	4.6	5.3	.7
10	52	F	8.8	11.6	24.9	13.3	5.3	4.9	-.4
11	56	F	10.4	9.7	9.6	-.1	3.8	3.5	-.3
12	73	F	9.3	12.3	27.0	14.1	5.1	6.2	1.1
13	49	M	11.4	14.4	11.6	-2.8	4.8	5.0	.2
14	41	F	9.6	8.4	10.1	1.7	5.1	4.8	-.3
15	56	M	8.5	13.6	19.4	5.8	6.0	6.0	0
16	39	F	9.4	3.4	7.8	4.4	3.4	3.6	.2
17	59	F	9.2	8.6	16.3	7.7	5.7	6.1	.4
18	66	M	12.8	13.1	6.2	-6.9	5.1	4.5	-.6
19	57	F	7.8	6.1	14.0	5.9	5.0	4.3	-.7
20	38	F	8.0	9.2	17.9	8.7	6.4	6.0	-.4
21	50	F	7.8	9.0	9.0	0	5.8	5.7	-.1
						10*			2*

* Number of patients with significant increases

The intramuscular injection of TSH induces an increased avidity for iodine and a discharge of hormones from the gland.[11] As Jefferies emphasized and our data show, both properties should be measured when estimating thyroid reserve, since they may vary independently.

"Normal thyroid reserve" in treated patients implies that despite partial destruction of the gland the thyroid may continue to function normally. "Low reserve" suggests that some degree of hypothyroidism may be imminent. However, no prospective data have yet been obtained to confirm this speculation.

In our study thyroid reserve was

studied in patients with Graves' disease who had been returned to the euthyroid state either by surgery or radioactive iodine therapy. More than half the patients in both groups exhibited low thyroid reserve. This failure to respond to injected TSH indicates that the thyroid remnant was receiving maximal stimulation from an endogenous thyroid stimulator. Since no suppression tests nor assays for TSH or long acting thyroid stimulator (LATS) were obtained, we have no evidence whether the gland was responding to TSH or to the persistant autonomous stimulator of Graves' disease.

In 1955 Martin and Stanbury measured the response of the ^{131}I-treated thyroid gland to exogenous TSH eight months or more after therapy.[17] Two of their 12 patients had also undergone subtotal thyroidectomy prior to ^{131}I therapy and were hypothyroid when tested. Four of ten euthyroid

TABLE III
Surgically Treated

				3 Hour Uptake (%)			Serum PBI (mcg %)		
No.	Age When Studied	Sex	Years Since Therapy	Before TSH	After TSH	Change	Before TSH	After TSH	Change
1	42	F	5.9	8.2	21.3	13.1	5.2	5.5	.3
2	24	F	5.7	9.6	4.0	-5.6	4.5	5.3	.8
3	35	F	5.4	13.9	16.6	2.7	5.7	6.6	.9
4	32	M	5.7	7.2	10.0	2.8	4.2	4.7	.5
5	63	F	10.6	6.4	12.2	5.8	5.2	7.1	1.9
6	54	F	6.6	6.0	12.0	6.0	5.8	5.8	0
7	39	M	10.0	10.3	11.0	.7	3.4	3.7	.3
8	31	F	7.3	9.9	18.2	8.3	5.2	6.9	1.7
9	42	F	7.5	9.4	10.0	.6	6.3	7.5	1.2
10	28	F	11.5	7.5	10.6	3.1	4.6	4.7	.1
11	37	M	10.7	7.2	7.4	.2	4.1	4.3	.2
12	40	F	10.1	10.0	13.6	3.6	5.0	4.8	-.2
13	40	F	11.1	10.1	10.3	.2	5.1	5.9	.8
14	30	F	10.4	10.5	12.3	1.8	6.5	7.3	.8
15	41	M	13.2	6.5	10.0	3.5	4.3	4.8	.5
16	34	F	5.7	9.6	12.4	2.8	6.3	7.9	1.6
17	52	F	6.9	19.3	17.0	-2.3	5.8	6.0	.2
18	52	F	10.0	14.1	6.0	-8.1	10.0	11.0	1.0
19	22	F	11.3	10.3	10.0	- .3	6.1	7.7	1.6
20	41	F	13.0	9.7	11.8	2.1	5.3	6.6	1.3
						4*			7*

* Number of patients with significant increase

subjects had no significant response in either uptake or PBI, four patients had normal thyroid reserve as indicated by both measurements, while of the remaining two a significant increase in the PBI occurred in one and the uptake rose in the other.

The present study compares thyroid reserve after a considerably longer time following ^{131}I therapy and surgery. Martin and Stanbury's data indicate somewhat better thyroid function in the early months following treatment as compared to the reserve 5 to 15 years after therapy. However, Bronsky et al[18] have recently pointed out the statistical limitations of many studies implicating irradiation as an important factor in the late occurrence of hypothyroidism in Graves' disease.

Recent studies in rats have demonstrated inhibition of DNA synthesis in ^{131}I-irradiated glands and a shorter life span for these same cells.[19] Presumably the shortened individual cell life span as well as the impaired ability to proliferate accounts for the increasing hypothyroidism which appears to occur with time.[20-21] The reproducing capacity of thyroid cells may also be impaired by external irradiation; and a high mitotic index at the time of irradiation as in hyperthyroidism, presumably makes the cells more vulnerable. In attempts to decrease the incidence of hypothyroidism, pre-treatment with antithyroid drugs renders the thyroid cell relatively radioresistant correlated with decreased mitotic activity.[22] From present reports, little advantage seems to have been gained by this approach.[23] In fact, there is evidence to suggest that such treatment may have a carcinogenic effect in rats.[24]

One suggested approach is to decrease the total quantity of radiation, administering as little as one-half the present usual treatment dose. The patient may be maintained with iodine or antithyroid drugs until he becomes euthyroid.[25-27] Although the available followup does not permit conclusions, this method seems to offer some protection against hypothyroidism. The disadvantage of prolonging the hyperthyroid state with this system of therapy may more than outweigh the advantage of possible preservation of adequate thyroid function.

Even with the heavier dosage schedules, comparison between the two groups in our study show no functional difference after 5 to 15 years between the non-irritated and the sublethally irradiated follicles. From these observations we consider hypothyroidism occurring after five years to be related to the natural history of the disease and not the mode of therapy although latent radiation effects on cellular division could still become manifest. However, since hypothyroidism is known to occur as late complication of untreated Graves' disease, we may become more aware of this aspect of the natural history of the disease with the increased life expectancy and more precise means of study.

Treatment of diffuse toxic goiter by subtotal destruction of the thyroid requires at least temporary loss of thyroid reserve or remission does not take place. Only half of the patients in either group had any recovery of measurable reserve. This observation underlines the importance of close followup and continued medical supervision of all patients with Graves' disease regardless of the type of therapy.

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