EFFECT OF TSH ON THE 24-HR ^{131}I UPTAKE IN GRAVES' DISEASE

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That the thyroid gland in Graves' disease is responsive to exogenous thyrotropin (TSH) has been appreciated for some years. TSH augments the thyroidal iodide clearance (*1*), the 10-min accumulation gradient (*2*), the 1-, 2-, 4- and 6-hr radioiodine uptake (*1*) and the secretion rate of both labeled (*3,4*) and unlabeled (*5*) thyroid hormone. The 24-hr uptake of radioiodine, however, is not ordinarily affected by TSH (*1,2,5*), but in almost all cases studied the baseline value was markedly elevated above the normal range. It is doubtful whether glands with high uptakes are capable of much further response at all, irrespective of whether or not Graves' disease is present (*6*).

To gain some insight into the stimulatory reserve capacity in Graves' disease we therefore measured the response of the 24-hr uptake to thyrotropin in eight patients with this disorder; in all of them the baseline value was within normal limits. The diagnosis was made by (1) characteristic (albeit mild) clinical picture, (2) failure of the 2- and 24-hr radioiodine uptake to suppress following administration of *l*-triiodothyronine (*l*-T_3) for 3 days (*7*), (3) elevated protein-bound iodine (PBI) levels in six of the eight patients; (4) failure of TSH to stimulate suppressed tissue in serial scintigrams (thereby ruling out Plummer's disease) (*8*) and (5) typical morphologic changes in the one thyroid gland biopsied. One patient had infiltrative ophthalmopathy and ophthalmoplegia.

TABLE 1. COMBINED 7 DAY L-TRIIODOTHYRONINE SUPPRESSION TEST AND TSH STIMULATION TEST

Day	Procedure
1–2	Baseline ^{131}I (12 μCi) uptake (2 and 24 hr) and ^{125}I (100 μCi) scan.
2–5	*l*-T_3* 25 μg q 8 hr.
5	^{131}I (100 μCi)—2-hr uptake.
	TSH† 10 units i.m. after 2-hr uptake.
6	24-hr uptake and scan.
	^{131}I (200 μCi)—2-hr uptake.
7	24-hr uptake and scan.

* Cytomel, Smith, Kline & French, Inc.
† Thytropar, Armour.

MATERIALS AND METHODS

Baseline ^{125}I uptake and ^{125}I scans were performed followed by a 3-day *l*-T_3 suppression test, as described previously (*7*). Ten units of thyrotropin (Thytropar, Armour) were injected intramuscularly after the 2-hr postsuppression uptake, and the ^{131}I dose for the post-TSH uptake was given 18–22 hr later (Table 1).

RESULTS

In seven of eight cases, TSH provoked a brisk response in the 24-hr uptake (Table 2), comparable in magnitude to that seen in normal persons (*6*). In the seven patients in whom it was measured, the 2-hr uptake also rose. One patient showed a rise in the 2-hr uptake and a slight fall in the 24-hr uptake.

DISCUSSION

These findings are consistent with the known stimulatory effects of thyrotropin on iodine economy in diffuse toxic goiter (*1–5*). They suggest that the inability of previous investigators to demonstrate a rise in the 24-hr uptake was usually due to selection of patients for study with high baseline values. In other patients an increased turnover rate was misinterpreted as a lack of response because of failure to perform an early uptake determination. Our results corroborate the opinion of Greer and Shull (*4*) and of Goolden (*1*) that there does not appear to be any qualitative difference in responsiveness to thyrotropin between the normal thyroid gland and the diffuse toxic goiter.

There also seems to be no difference between the response of these patients with Graves' disease with

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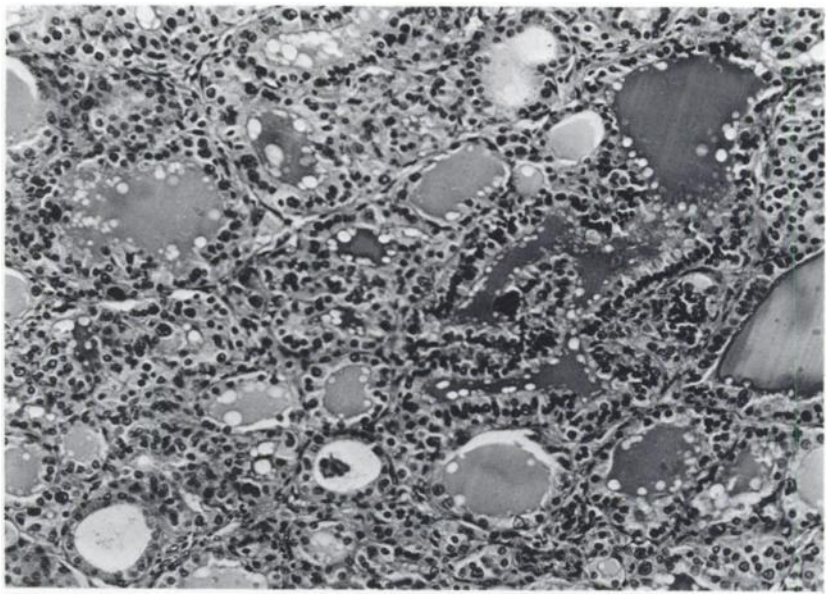

FIG. 1. Thyroidectomy specimen from patient AJ. Note papillation of lining epithelium, depletion and scalloping of colloid, increased height of epithelial cells, irregularity of size of epithelial cells and of follicles, and interstitial lymphocytic infiltration typical of diffuse toxic goiter. Iodides were administered preoperatively. Hematoxylin and eosin, × 208.

normal baseline uptakes and the response of most euthyroid patients with the infiltrative ophthalmopathy of Graves' disease (*9,10*). Werner's group, however, noted only a minimal rise in the 24-hr uptake in five of eight euthyroid patients with eye signs following administration of 10 units of TSH daily for 3 days (*11*). This dose provoked a marked discharge of unlabeled thyroid hormone from the gland. An increased turnover rate with augmentation by TSH of both iodide trapping and release of labeled hormone would result in little net change in thyroid counts at 24 hr and could explain these findings. The validity of this line of reasoning is suggested by the response of patient GS to TSH: The 2-hr uptake rose from 12% to 17% and the 24-hr uptake fell slightly from 31% to 28%. It is of interest that this patient was the only one in the series with infiltrative ophthalmopathy.

In all of our patients the degree of hyperthyroidism was mild, and in two patients the PBI levels were within the normal range. In one large series, the PBI was elevated (>7.6 μg%) in 97% of patients with diffuse toxic goiter (*12*). In each of the two patients, however, subsequent events substantiated the

TABLE 2. RESPONSE TO THYROTROPIN OF EIGHT PATIENTS WITH DIFFUSE TOXIC GOITER

				^{131}I uptake*						
				Baseline		After $I\text{-}T_3$		After TSH		
Patient	Age	Sex	PBI (μg/100 ml)	2 hr	24 hr	2 hr	24 hr	2 hr	24 hr	Remarks
EA	47	F	7.9	10	30	6	25	25	68	4-yr history, controlled by Tapazole, off drug 10 mo, recurrence.
SL	78	F	11.1	7	27	7	27	—	46	Mild hyperthyroidism; T_3 resin uptake 39%.
CD	58	F	6.8	5	26	4	22	27	83	Subtotal thyroidectomy 25 yr previously for hyperthyroidism, recent recurrence; subseqeunt storm controlled by Lugol's sol'n and Tapazole followed by ^{131}I therapy with good response.
FF	57	F	10.4	13	30	15	31	28	69	Masked hyperthyroidism.
AJ	39	F	7.4	10	29	11	34	34	61	3-yr history, controlled by Tapazole, off drug 3 mo, recurrence; subsequent thyroidectomy-path.: diffuse hyperplasia (Fig. 1).
JG	59	F	10.3	9	38	13	43	41	67	4-yr history; T_3 resin uptake 39.4%; subsequent response to ^{131}I therapy.
EN	41	F	10.4	11	35	14	37	20	49	1-yr history, mild hyperthyroidism.
GS	49	M	9.6	7	24	12	31	17	28	3-mo history including ophthalmoplegia and infiltrative ophthalmopathy.

* Normal range: 2 hr < 18%; 24 hr 10–40%.

impression of diffuse toxic goiter: patient CD went into thyroid storm following laminectomy and excision of a meningioma, having been on Tapazole for only 3 days; she responded to Lugol's solution, Tapazole, supportive care and subsequently to ^{131}I therapy. Patient AJ underwent thyroidectomy, and the histologic findings were typical of Graves' disease (Fig. 1). Excessive secretion of *l*-T_3 but not of thyroxin could account for the normal PBI in these two patients despite clinical hyperthyroidism (*13*).

The response of these patients to TSH indicates that the thyroid gland is not autonomous in Graves' disease, despite failure of the 2- and 24-hr uptakes to suppress after administration of thyroid hormone. Since the disorder may occur or persist after destruction of the pituitary (*14*), a nonsuppressible thyroid-stimulating substance of nonpituitary origin (such as LATS) appears to offer the most reasonable explanation for the pathogenesis of the disease.

These results provide an additional diagnostic point of differentiation between diffuse toxic goiter and Plummer's disease. The latter disorder is always associated with suppressed normal tissue (*8*), and there is no response to TSH by the hyperfunctioning tissue (*15*). In Graves' disease, on the other hand, suppressed tissue is not seen and there is usually a marked increase in the 24-hr uptake following administration of TSH if the baseline value is normal to begin with.

SUMMARY

Eight patients with Graves' disease with normal 2- and 24-hr ^{131}I uptakes were given 10 units of TSH intramuscularly. A marked increase in the uptakes was noted in seven, and an augmented turnover rate in the eighth. Although the series is small, these findings confirm previous observations which suggest that the thyroid gland is not autonomous in Graves' disease.

ADDENDUM

Since this paper was submitted for publication, we have studied one additional patient with mild hyperthyroidism. Two and 24-hr uptakes were 7% and 19%, respectively; after *l*-T_3 they were 5% and 15%; and after TSH they were 19% and 43%. Serial scans did not change. Baseline PBI was 5.7 μg%, serum T_4 was 9.1 μg% and T_3 resin uptake was 36%. These findings are similar to the results reported in this paper.

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