JOURNAL OF NUCLEAR MEDICINE 8:758-768, 1967

The Effect of TSH on the Solitary Hyperfunctioning Thyroid Nodule[1]

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In 1913 Plummer (1) differentiated toxic nodular goiter from diffuse toxic goiter (Graves' disease) on clinical grounds and noted that nodular goiter was associated with a mild atypical thyrotoxicosis and an absence of exophthalmos. In 1947, Cope, Rawson and McArthur (2) first demonstrated that a solitary thyroid nodule, as opposed to a multinodular goiter, was capable of producing the type of hyperthyroidism described by Plummer. They showed that when this lesion accumulated all of an administered tracer dose of ^{131}I, it was associated with cellular and functional atrophy of the remainder of the gland. The anatomic and functional atrophy of the extranodular tissue was assumed to be the result of TSH reduction, secondary to pituitary suppression by excess thyroid hormone released from the nodule. The clinical and laboratory features associated with the solitary hyperfunctioning thyroid nodule have been well described and need not be reviewed here (3-6).

These lesions are easily recognized by their characteristic accumulation of virtually all of the administered radioiodine on a thyroid scan (Fig. 1A). Nearly all authors have held that these nodules are autonomous in function and independent of pituitary TSH, since thyroid hormone administration does not suppress the uptake of iodine by the gland as a whole, or alter the appearance of the thyroid scan (3-9) (Fig. 1B). The rise in overall uptake commonly seen following exogenous TSH administration, has been attributed largely to stimulation of suppressed thyroid tissue (Fig. 1C), but there has been less certainty concerning the response of the nodule itself. Miller states that it is "much less than that of the suppressed normal tissue" (4) and Dorta describes the response as little or none (10). Skillern *et al* (3) and Seed (11) believe that hyperfunctioning adenomas are responsive to thyrotropin, inasmuch as they advocate administration of TSH to patients with low or low-normal uptakes prior to a therapeutic dose of ^{131}I. Fellinger noted a rise in ^{131}PBI following TSH administration and

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[1]Presented at the 13th Annual Meeting, Society of Nuclear Medicine, Philadelphia, Pennsylvania, June 22-25, 1966.

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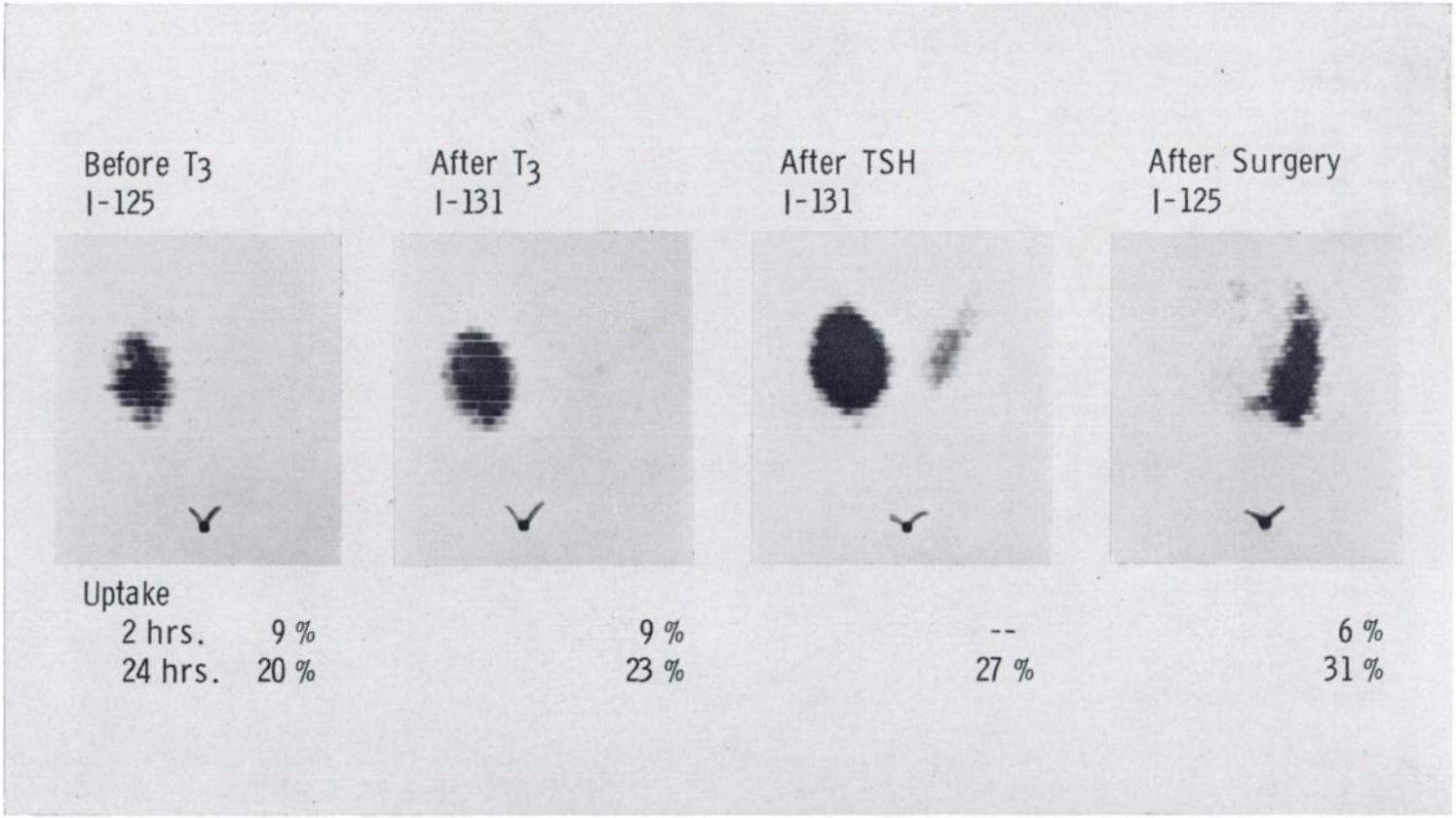

Fig. 1. (Case 8) Thyroid scintigrams show a typical solitary hyperfunctioning nodule in the right lobe. A. Initially, all the visible iodine is in the nodule. B. Following triiodothyronine, 25 ug every 8 hours for 3 days, the scan is unchanged. C. Following 10 units of TSH, the previously suppressed left lobe is visualized. Ratio of external (corrected) counts over nodule is 2.1, left lobe 13.1. Ratio of administered doses is 2.5. This indicates TSH stimulation of the extranodular portion of the gland but not of the nodule. D. Following surgical removal of the nodule, the left lobe has resumed normal function.

concluded that the nodule had responded with a release of hormone, although no evidence was presented to show that this effect was on the nodule itself and not on the remainder of the gland (12).

Since previous studies of TSH responsiveness have been inconclusive, due to lack of discrete quantitative data concerning the nodule and the suppressed tissue, it was decided to measure the effect of TSH on the hyperfunctioning nodule separately from the extranodular tissue by means of differential uptake studies. By the utilization of a highly collimated external counting system it was possible to measure ^{131}I activity in a small portion of the thyroid relatively free from interference by the ^{131}I in the remainder of the gland.

MATERIALS AND METHODS

Seventeen consecutive patients in whom the thyroid scan showed virtually all function in one ("hot" nodule) area were selected for study. All but two of these patients had single nodules clinically. One patient (Case #17) had two equally active nodules (Fig. 2) and one patient had a diffusely enlarged gland with all of the iodine concentrated in one area (Case #10, Fig. 3). At the time of the study, none of the patients was receiving drugs which interfere with measurement of thyroid uptake. Case #5 had been previously treated with ^{131}I. Initial uptakes and scans were performed with 12 μc of ^{131}I and 100 μc of I-125, respectively (13). Triiodothyronine[1] 25 ug was then given every 8 hours for four days and the uptake and scan repeated with ^{131}I on the fourth day (14). Following this two-hour uptake, 10 units of TSH[2] were administered intramuscularly and 24 hours later the radioiodine studies were again repeated with ^{131}I. Corrections for residual iodine in the gland were made on the basis of the 8.05 day physical half-life of ^{131}I. Increasing doses of ^{131}I were used to minimize errors resulting from the prior administration of iodine.

All doses of ^{131}I were given in liquid form and counted prior to administration. In addition, point counts were taken at the time of the 24-hour uptakes, before and after TSH administration over the nodule and over several points in the neck, where it was anticipated (correctly in all cases) that the non-visualized thyroid tissue might be. The points were marked with a skin marker. Scans were performed with a commercial scanner[3] with a 3″ × 2″ sodium iodide crystal and a 31-hole focused collimator and the pulse height analyzer set to accept only the 364 ± 60 KeV photon of ^{131}I. The point counts were taken by a scaler from the same scanning device. Counting error was less than 5%. With this highly collimated counting system, a point source in water 6 mm from the central axis in the focal plane would produce only 10% of the counts obtained on the axis. Since all nodules were at least 3 cm in diameter, the maximum contribution to any point count over a nodule from iodine in adjacent tissue would not exceed 1.1%.

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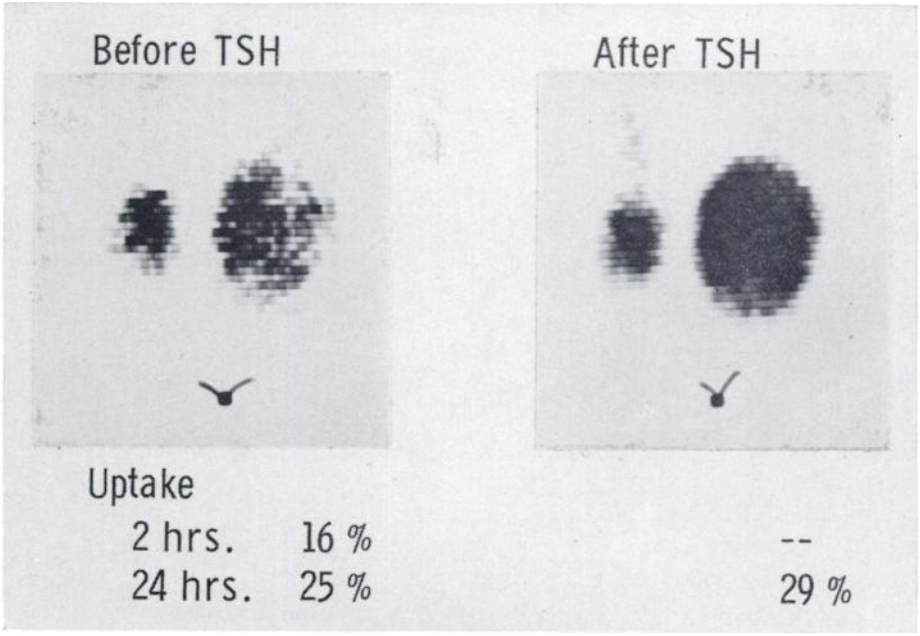
[1]Cytomel® (Smith, Kline & French).

[2]Thytropar® (Armour).

[3]Picker Magnascanner II.



Figs. 2A and 2B

Fig. 2. (Case 17) A. Thyroid scintigram showing a hyperfunctioning nodule in each lobe. B. Following TSH, suppressed tissue is demonstrated in both lobes.

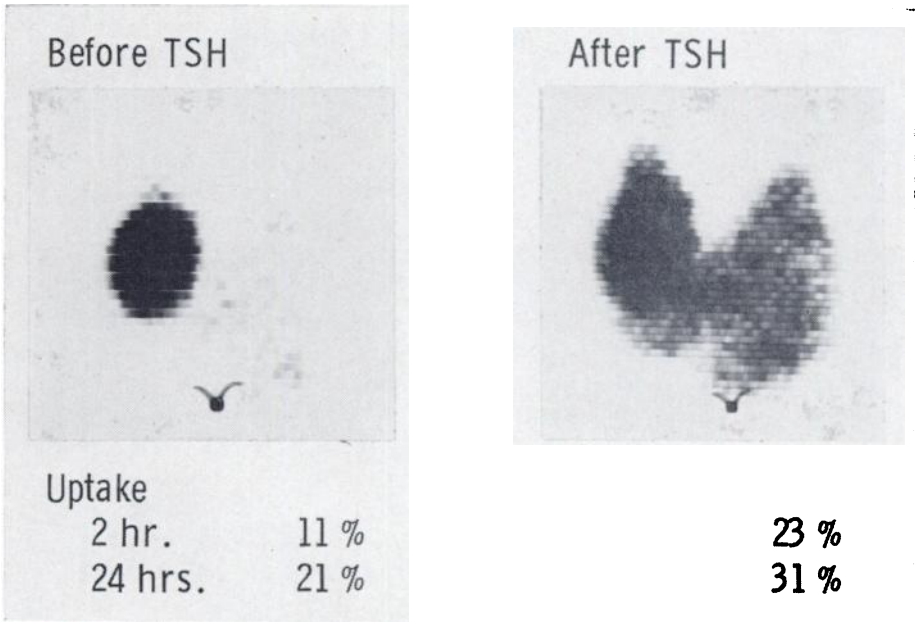


Fig. 3. (Case 10) A. Thyroid scintigram with a "hot" area in the right lobe of a diffusely enlarged gland containing no palpable nodules. The left lobe is faintly seen. B. At surgery, a large nodule which corresponded to the hot area was found. Microscopically there were multiple small nodules throughout the gland, indistinguishable from the large nodule.

Furthermore, any such contribution would overestimate the response of the nodule to TSH.

RESULTS

Table I shows the effect of triiodothyronine and TSH on ^{131}I uptake. It should be noted that there was little correlation between initial uptake and the clinical status of the patient. In most cases (14/17) the uptake was normal and five out of seven clinically hyperthyroid patients had normal uptakes. Two euthyroid patients had low initial uptakes although one of these (Case #5) had been previously treated with ^{131}I. Only one patient (Case #15) showed significant suppression of the 24-hour uptake following triiodothyronine, but the two hour uptake rose slightly and the nodule was not stimulated by TSH. In 13/14 patients there was an increase in the post-triiodothyronine two hour uptake. The rise in overall uptake following TSH was variable, but both the scan and external counting showed stimulation of extranodular tissue by TSH in all but one patient.

The effect of suppression and stimulation on the thyroid scan is shown in Table II. As expected, none of the patients showed any change in the scan following triiodothyronine. The post-TSH scans indicated the presence of sup-

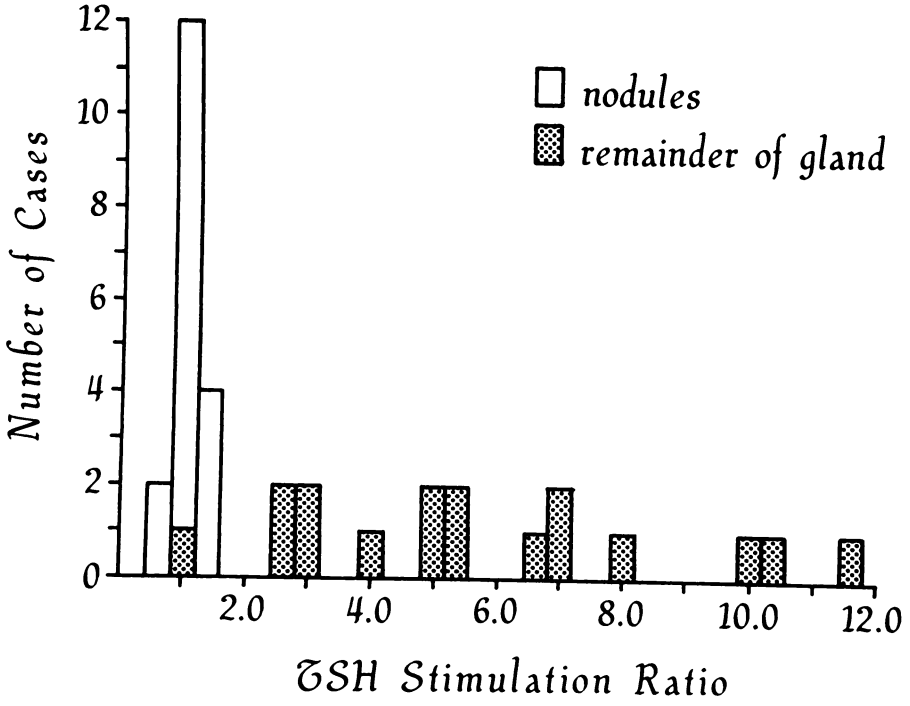


Fig. 4. The TSH stimulation ratios of the hyperfunctioning nodules cluster around 1.0 which indicates no TSH response (mean 1.03 ± .306 S. D.). The extranodular portions of the glands show stimulation in all but one case.

TABLE I

EFFECT OF TRIIODOTHYRONINE AND TSH ON THE UPTAKE[1] OF IODINE IN PATIENTS WITH A SOLITARY HYPERFUNCTIONING THYROID NODULE

Case	*Sex*	*Age*	*Clinical Impression*	*Initial Uptake* 2 hrs %	*Initial Uptake* 24 hrs %	*Uptake after Triiodothyronine*[2] 2 hrs %	*Uptake after Triiodothyronine*[2] 24 hrs %	*Uptake after TSH*[3] 2 hrs %	*Uptake after TSH*[3] 24 hrs %
1	F	52	hyperthyroid	16	28	30	36	—	56
2	F	40	euthyroid	20	23	—	23	—	28
3	F	56	euthyroid	19	43	—	38	—	58
4	F	32	euthyroid	18	45	19	42	—	54
5	M	71	euthyroid	6	9	8	13	—	27
6	F	44	euthyroid	6	19	11	26	—	39
7	F	50	euthyroid	11	21	—	17	—	29
8	F	27	euthyroid	9	20	9	23	—	27
9	F	26	euthyroid	12	28	17	33	—	58
10	F	50	euthyroid	11	21	18	18	23	31
11	F	40	euthyroid	9	25	15	33	—	48
12	F	36	euthyroid	6	8	9	19	—	45
13	M	69	hyperthyroid	14	27	16	36	11	37
14	F	39	hyperthyroid	9	15	12	16	—	36
15	M	57	hyperthyroid	16	44	22	25	—	32
16	M	64	hyperthyroid	6	17	8	27	—	44
17	F	39	hyperthyroid	16	25	18	28	—	29

[1]Uptake refers to overall uptake of whole gland. Upper normal limit: 2 hrs 20%, 24 hrs 40%. Lower normal limit: 10% at 24 hrs.
[2]Cytomel® 25 ug q.8 h. for 4 days, ^{131}I on 4th day.
[3]Thytropar® 10 u. I. M.

TABLE II

EFFECT OF TRIIODOTHYRONINE AND TSH ON THE THYROID SCAN OF PATIENTS WITH A HYPERFUNCTIONING THYROID NODULE

Case	*Initial Scan*		*Scan after Triiodothyronine*[1]	*Scan After TSH*[2]
	^{131}I in Nodule	*^{131}I in Remainder of Gland*	*Hypofunctioning Area in Nodule*	*Increase in ^{131}I Outside of Nodule*
1	nearly all	slight	yes	unchanged	yes
2	all	none	yes	unchanged	yes
3	nearly all	slight	no	unchanged	yes
4	nearly all	slight	no	unchanged	yes
5	all	none	no	unchanged	yes
6	nearly all	slight	yes	unchanged	yes
7	all	none	no	unchanged	yes
8	all	none	no	unchanged	yes
9	most	some	no	unchanged	yes
10	nearly all[3]	slight	no	unchanged	yes
11	all	none	yes	unchanged	yes
12	most	some	no	unchanged	yes
13	all	none	yes	unchanged	yes
14	all	none	yes	unchanged	yes
15	all	none	yes	unchanged	yes
16	nearly all	slight	no	unchanged	yes
17	all[4]	none	yes	unchanged	yes

[1]Cytomel® 25 ug q.8 h. for 4 days, ^{131}I on 4th day.
[2]Thytropar® 10 u. I. M.
[3]Diffusely enlarged gland with nearly all ^{131}I concentrated in 1 area.
[4]2 nodules contained all the ^{131}I.

TABLE III

EFFECT OF TSH ON THE 24 HOUR UPTAKE OF IODINE IN PATIENTS WITH A HYPERFUNCTIONING THYROID NODULE

Case	^{131}I Administered Dose After TSH / Before TSH		^{131}I External Counts After TSH / Before TSH		Ratio of External Counts / Ratio of Administered Doses	
	Counts	Ratio	Nodule[1]	Remainder of Gland[2]	Nodule	Remainder of Gland
1	238,081 80,144	3.0	2.9	6.7	1.0	2.3
2	155,181 42,312	3.7	5.6	11.3	1.6	3.1
3	223,384 110,225	2.0	2.2	4.6	1.1	2.3
4	160,500 34,604	4.6	4.6	5.4	1.0	1.2
5	155,057 37,749	4.1	6.5	28.0	1.6	6.8
6	236,518 74,563	3.2	2.8	34.0	0.88	10.6
7	161,919 84,399	1.9	2.4	11.9	1.3	6.3
8	207,887 81,700	2.5	2.1	13.1	0.84	5.2
9	152,588 52,158	2.9	1.4	8.0	0.48	2.8
10	263,555 103,891	2.5	2.0	14.1	0.80	5.6
11	104,793 51,867	2.0	2.5	14.3	1.3	7.2
12	164,586 51,782	3.2	2.8	15.8	0.88	4.9
13	147,247 50,137	2.9	1.7	33.5	0.59	11.5
14	240,672 85,850	2.8	3.2	28.6	1.1	10.2
15	213,783 84,143	2.5	2.9	19.8	1.2	7.9
16	167,996 88,464	1.9	1.6	7.5	0.84	3.9
17	243,538 83,714	2.9	3.0	16.6	1.0	5.7
Mean ± S.D.					1.03 ± .31	5.7 ± 3.1

1. Following TSH, the increase in counts over any nodule does not significantly exceed the increase expected from the larger dose of ^{131}I.

2. The remainder of the gland shows an increase in external counts in excess of what would be expected from the larger dose of ^{131}I after TSH.

pressed tissue in all cases, but it was not possible to accurately determine from the scan alone, without the counting data, whether there had been any TSH effect on the nodule. Eight of the patients showed small, non-functioning areas within the nodule. These areas may represent cystic, hyaline or hemorrhagic degeneration and have been previously described (4, 5).

Table III shows the results of the external collimated point counting. It was reasoned that if there were no response to TSH, the ratio of counts over any portion of the gland, before and after TSH, should be the same as the ratio of the administered doses of ^{131}I. For example, if 25,000 counts/min were administered before TSH and 100,000 counts/min after TSH, and if there were 2,500 counts/min over a point in the thyroid gland from the pre-TSH ^{131}I and 10,000 net counts/min over the same point from the post-TSH ^{131}I, it could be concluded that this area did not respond to TSH, inasmuch as, the fourfold increase in counts resulted from a fourfold increase in the administered dose.

The last two columns in Table III express the ratio of the observed counts to the ratio of the administered doses such that 1.0 is indicative of no response. In the above example, a fourfold increase in counts ÷ a fourfold increase in dose = 1.0. This value can be called the TSH stimulation ratio. The mean of the TSH stimulation ratios was 1.03 for the nodules (S.D. 0.306, Column 5) and 5.7 for the remainder of the gland (S.D. 3.1, Column 6). The mean value for the nodules, 1.03, does not differ significantly from the predicted mean of 1.0 which would be found if there were no response to TSH. Therefore, the nodules as a group did not respond to TSH. On the other hand, the mean value of 5.7 for the remainder of the gland does significantly exceed 1.0 and is indicative of stimulation of the extranodular portion of the gland ($t = 6.31$, $p < .001$). Figure 4 shows the distribution of the TSH stimulation ratios.

DISCUSSION

Although many workers have shown that the solitary hyperfunctioning thyroid nodule is not suppressed by thyroid hormone administration, the TSH responsiveness of this lesion has not previously been studied quantitatively. That nonsuppressibility by thyroid hormone does not necessarily imply unresponsiveness to TSH is well illustrated by Graves' disease in which the gland is not suppressed by thyroid hormone administration and yet will respond to TSH. This response, however, is abnormal, since the peak effect occurs earlier than in the normal patient and more TSH is required for its demonstration (15-19). Further evidence that the thyroid in Graves' disease will respond to TSH is provided by the clinical observation that the thyroid gland of patients overtreated with antithyroid drugs will enlarge, presumably due to an increase in pituitary TSH, secondary to the excessive drug-induced reduction of thyroid hormone synthesis.

Similarly, the ability of the hyperfunctioning nodule to respond to TSH cannot be predicted from its failure to be suppressed by thyroid hormone. In toxic nodular goiter, the presence of physiologically suppressed normal thyroid tissue complicates the study of TSH responsiveness, since any total measurement measures both diseased and normal portions of the gland. With a large single nodule this difficulty can be almost completely overcome, since with a highly collimated

system it is possible to perform external studies of uptake and clearance on the nodule alone. Of course, there will always be a small unavoidable error caused by ^{131}I in tissue superficial or deep to the nodule. Also, the necessity for accurate probe placement introduces another possible source of error which can be minimized by careful attention to positioning the patient and the detector.

Using this method, 10 units of TSH did not produce a rise in the 24 hour accumulation of iodine by the nodule, whereas, a normal gland would show a considerable response to this dose.[1] In Graves' disease the 24 iodine uptake following TSH is variable, but usually unaltered, since the maximum response is observed somewhat earlier. Two hour uptakes after TSH were not routinely performed in this study; therefore, an early effect cannot be ruled out. In addition, it is always possible that additional stimulation with larger doses of TSH might have produced a rise in the 24 hour uptake.

It appears that the increase in the 24 hour uptake which commonly occurs when a 10 unit dose of TSH is given to patients with toxic nodular goiter is due entirely to stimulation of previously inactive tissue. In view of this, the recommendation that TSH be administered to increase a low iodine uptake by the nodule prior to ^{131}I therapy (3,11), would seem unwarranted. In fact, TSH might be harmful in this situation, since it would have no effect on the nodule, but would stimulate the normal tissue to accumulate ^{131}I and thereby increase the risk of myxedema.

Although stimulation by TSH would have been considered insignificant in 7 of the 17 cases if judged by a standard TSH test (21), the thyroid scan with external counting demonstrated extranodular stimulation in 16 of 17. This indicates that the usual criteria for a positive 10 unit TSH test do not apply to solitary hyperfunctioning nodules. Thyroid scans are necessary to demonstrate suppressed tissue and external point counting is necessary to judge the magnitude of the response.

An unusual finding in these patients is the tendency toward higher iodine uptakes following ingestion of triiodothyronine. Interestingly enough, the 24 hour conversion ratio also has been observed to rise in some instances following triiodothyronine in solitary nodular goiter (10). A small, but statistically significant rise in the early rate of uptake of ^{131}I in Graves' disease also has been observed following the administration of thyroxine (22). These findings are unexplained, but the effect of triiodothyronine on the blood TSH level is currently under investigation in our laboratory.

SUMMARY

1. A method is described for evaluating the iodine accumulation function of solitary thyroid nodules independent of the remainder of the gland.

2. The 24 hour uptake of ^{131}I by the solitary hyperfunctioning thyroid nodule is not increased by 10 units of TSH.

3. Measurement of overall uptake following TSH is of limited value in demonstrating suppressed thyroid tissue in the presence of a hyperfunctioning

[1] 0.003 to 0.025 USP units/kg of TSH produces a maximum increase in iodine uptake by the normal thyroid gland (20).

nodule, but thyroid scanning and external counting will regularly indicate its presence.

4. TSH should never be administered prior to ^{131}I therapy of a toxic, benign, solitary thyroid nodule (except for diagnostic purposes).

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