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A Three Day, Double Isotope, l-Triiodothyronine Suppression Test of Thyroid Autonomy[1,2]

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In 1965 Werner and Spooner described a test of thyroid autonomy which has found wide acceptance in medical practice (1). They found that administration of l-triiodothyronine (T-3) in doses of 75 to 150 mcg daily, for seven days, suppressed the thyroid uptake of ^{131}I in normal persons and in most patients with nontoxic goiter. Little or no change occurred in patients with diffuse toxic goiter (Graves' disease) and toxic nodular goiter. These findings have been amply confirmed by others (2-17). Thyroid extract and l-thyroxine have a similar action.

In these tests:

(1) T-3 is administered for two to seven days prior to the second uptake;

(2) The uptake is usually determined at 24 hours only;

(3) Thyroid scanning is not usually done in conjunction with the uptakes, and when done, only one isotope (^{131}I) is employed for both pre- and post-T-3 scans.

A number of deficiencies in the original method became apparent when the technique was applied to evaluation of localized areas of thyroid autonomy:

(1) Hormone administration for seven days prior to the second uptake makes testing of hospitalized patients too time consuming to be practical;

(2) The use of only one isotope in goitrous patients with nonuniform iodine deposition produees considerable difficulty in accurate interpretation of localized areas of poor suppression on the second scan because of residual radioactivity from the initial dose;

(3) The use of 100 microcuries of ^{131}I for the initial scan necessitates an equal or greater dose for the second scan, which results in an unduly high radiation dose to the thyroid gland.

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We therefore investigated a three day, double isotope (^{125}I and ^{131}I) method for evaluation of thyroid autonomy by hormonal suppression. The time of three days was chosen because pituitary depletion of TSH is effected within 36 to 48 hours of onset of thyroid hormone feeding (18). A two day suppression test has proven workable in practice (5), but a high dose of T-3 (300 mcg/day) was employed. We felt that the additional day of hormone administration might avoid spurious results because of incomplete depletion of pituitary TSH in some cases, if smaller doses of T-3 were given. A three day test, using 100-150 mcg of T-3/day has been shown to be practicable (12, 17).

In the past, little attention has been paid to the importance of coincident thyroid scanning with the T-3 suppression test. Iodine-125 is normally employed for the initial scan in our hospital, because its deposition can be resolved with a higher degree of accuracy than can ^{131}I (19). The second scan is done with ^{131}I. By means of a pulse height analyzer, the 364 KeV photons of ^{131}I can be separated from the 27.4 KeV photons of the tellurium daughter of ^{125}I, with only 5.6% scatter of the higher energy photons into the ^{125}I window. There is no scatter of ^{125}I into the ^{131}I window. In performing the radioiodine uptakes, the soft ^{125}I (tellurium) x-rays are screened out of the detection probe by a $\frac{1}{16}''$ lead filter. Since our initial uptake is performed with 12 microcuries of ^{131}I and the scan with 100 microcuries of ^{125}I, less than 1% of the counts in the ^{125}I window are due to ^{131}I contamination on the initial scan[1] and no ^{125}I is seen on the (second) ^{131}I scan. The concept of the double isotope suppression test was first proposed by Levy *et al* (20).

METHODS AND MATERIALS

The initial thyroid uptake was performed with approximately 12 microcuries of ^{131}I given in 20 cc of water and counted on a beeswax block. Neck counts were performed at 2 and 24 hours, at a crystal-to-neck distance of 25 cm and thigh counts subtracted to yield the "thyroid uptake." At the conclusion of the two hour uptake, approximately 100 microcuries of ^{125}I were administered by mouth. This drink was also counted.[2] Twenty-four hours later the ^{125}I thyroid scan was performed at the 27.4 KeV photopeak window, using a 3 × 2 inch sodium iodide crystal (Picker Magnascanner).

For the 3-day suppression test, 25 micrograms of T-3[3] were given every 8 hours for 4 days, and on the fourth day, approximately 100 microcuries of ^{131}I were administered orally. Two and 24-hour uptakes were performed and a thyroid scintigram was done at 24 hours at the 364 KeV photopeak. All thyroid scans were performed with a 31-hole focusing collimator. Corrections for residual radioactivity in the gland were made assuming an effective half-life of 7.6 days.

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[1] $\frac{1}{100} \times \frac{12}{.985} \times \frac{.91}{.985} \times .056 = .0062$

[2] Less than 1% of the ^{125}I is present as ^{126}I, the principal photons of which are 382 KeV and 650 KeV and are detectable by the uptake probe. If not accounted for, this could result in erroneously high 24-hour uptakes by up to 10%. These ^{126}I counts are, therefore, added to the counts in the ^{131}I standard.

[3] Cytomel(R) (Smith, Kline and French, Inc.)

TABLE I

EFFECT OF *l*-TRIIODOTHYRONIME ON THYROID UPTAKE IN PATIENTS WITH UNIFORM SUPPRESSION ON SCINTIGRAM[1]

Diagnosis	*Initial Uptake 2 hr*	*Uptake 24 hr*	*Post T-3 2 hr*	*Uptake 24 hr*	*% fall in 24 hr uptake*	
Normal	13	37	6	16	56	
"	16	37	8	17	54	
"	7	21	–[2]	4	83	
"	17	38	5	15	60	
"	19	40	4	10	75	
"	28	40	9	13	67	
"	19	27	5	9	65	
Mean						66%
Nonfunctioning nodule[3]	17	42	10	19	47	
"	9	24	—	11	54	
"	7	15	—	11	28	
"	8	22	4	7	71	
"	10	26	—	13	50	
"	14	37	—	9	75	
Mean						56%
Diffuse non toxic goiter[4]	8	36	–	4	89	
"	8	13	–	6	54	
"	12	40	5	9	78	
"	33	45	9	23	50	
"	15	33	4	7	79	
"	16	32	8	23	30	
"	13	36	8	17	53	
"	7	19	5	7	62	
"	16	41	–	17	57	
"	5	14	4	8	42	
"	10	19	–	7	65	
"	5	9	6	7	28[5]	
"	14	22	5	3	86	
"	5	33	–	9	72	
"	12	32	5	9	71	
"	9	19	–	6	69	
"	15	38	8	17	56	
"	8	27	8	15	44	
"	15	52	13	22	58	
Mean						62%

TABLE I—CONTD.

EFFECT OF *l*-TRIIODOTHYRONINE ON THYROID UPTAKE IN PATIENTS WITH UNIFORM SUPPRESSION ON SCINTIGRAM[1]

Diagnosis	*Initial Uptake 2 hr*	*Uptake 24 hr*	*Post T-3 2 hr*	*Uptake 24 hr*	*% fall in 24 hr uptake*	
Suppressible functioning nodule[3]	14	39	7	17	57	
"	11	25	7	13	48	
"	6	16	–	6	63	
"	8	20	–	6	71	
"	8	23	–	14	40	
"	4	12	3	7	44	
"	5	14	–	7	55	
"	6	16	4	6	66	
Mean						56%
Mixed nodule[6]	10	25	5	14	44	
"	4	7	4	6	13[5]	
"	6	23	–	9	62	
Hashimoto's disease	18	37	8	10	74	
"	10	28	7	10	65	
Post-op hyperplasia	29	11	6	4	61	
"	8	19	7	9	51	
"	13	29	–	19	36	
Mean						56%
Total 46					Mean	59.5%

Range of Normal Uptakes: 2 hours < 20%; 24 hours 10-40%

[1]2nd Uptake begun on fourth day of hormone administration.

[2]Indicates not done.

[3]Thyroid gland otherwise normal.

[4]Includes colloid and multinodular goiters, cause unknown.

[5]Not included in mean (see text).

[6]Mixed non-functioning and functioning (Suppressible) areas.

In selected individuals, counts over various portions of the thyroid gland were performed after the second scan with the 31-hole focusing collimator as follows: With the window centered about the 364 KeV photopeak, one minute counts were taken on a scaler leading from the analyzer of the scanner. Without moving the probe, the amplifier and analyzer were then changed to record the counts at the 27.4 KeV photopeak. One minute counts were again taken. The probe was then moved to other positions over the thyroid gland and the $^{131}I/^{125}I$ counts obtained. As a rule, 600 to 5,000 net counts were recorded in a minute at 4 to 6 points over the gland. The "point count" ratio was expressed as $\frac{\text{net } ^{131}I \text{ counts.}}{\text{net } ^{125}I \text{ counts.}}$ The maximum ratio was compared with the average of the ratios elsewhere in the gland for each patient.

One hundred and eleven patients with a variety of thyroid disorders and seven normal persons were studied by this method. These patients were selected from patients referred to the Isotope Unit over a 3½ year period, except that 26 patients with autonomous ("hot") nodules were consecutive patients with this disorder. The diagnosis of hyperthyroidism, euthyroidism or hypothyroidism was made in each case on clinical grounds, supported by conventional laboratory studies.

In patients with autonomous nodules only, 10 units of TSH (Thytropar(R), Armour) were given intramuscularly, after the second (post-T-3) two hour uptake. The post-TSH uptake and scan were begun at the conclusion of the T-3 study.

RESULTS

Normals and Suppressible Non-Toxic Goiter (Table I)

In all of these 46 patients, uniform suppressibility was demonstrated by means of pre- and post-suppression scintigrams and confirmed by point-count ratios in 17 patients. Although some suppression could be demonstrated when the initial 24 hour uptake was less than 11%, the degree of fall was minimal in 2 of 3 cases. If the original uptake was between 11 and 15%, the mean fall was 47% of the initial value; if the initial uptake was between 16 and 29%, the mean fall was 59.5%. The mean fall in uptake was 59.5% in patients with initial uptakes of 30% or more.

Of the patients in this group with initial 24 hour uptakes of 9% or greater, 28 of 29 showed a decrease in the two-hour uptake.

In 98% of the patients with initial 24 hour uptakes of 16% or more, the fall in the 24 hour uptake was more than 30% of the initial value (Table II).

Untreated Diffuse Toxic Goiter (Table III)

The majority of these patients showed a rise in the 24 hour uptake; in only three did the uptake fall (by 9%, 11% and 16% of initial values). The two hour uptake rose in nine of 10 patients. Variable results were found in nine patients treated for the disease with drugs, radioiodine or surgery (Table IV).

In four patients with eye signs of Graves' disease (infiltrative ophthalmopathy), but without overt thyrotoxicosis, the results were also variable (Table V).

TABLE II

FALL IN 24 HOUR THYROID UPTAKE AFTER ADMINISTRATION OF T-3 FOR 3 DAYS IN PATIENTS WITH SUPPRESSIBLE GLANDS.

% of fall in 24 hour uptake from initial value[1]	*No. of cases*	*% of total*	*Cumulative % of total*
<29%	1	2%	2%
30–39	2	4%	6%
40–49	7	15%	21%
50–59	13	28%	49%
60–69	11	24%	73%
70–79	9	20%	93%
80–89	3	7%	100%
90–99	0	0	100%
Total	46		100%

[1]Excludes 2 cases with initial 24 hour uptake of < 11%.

TABLE III

EFFECT OF *l*-TRIIODOTHYRONINE ON THYROID UPTAKE IN PATIENTS WITH UNTREATED DIFFUSE TOXIC GOITER[1]

Initial 2 hr	*Uptake 24 hr*	*Post-T3 2 hr*	*Uptake 24 hr*	*% fall in 24 hr uptake*
11	39	18	40	rise
15	42	19	38	9
15	35	22	31	11
12	33	26	54	rise
14	24	—	33	rise
7	22	9	22	0
19	41	22	40	0
50	43	52	48	rise
47	57	—	69	rise
18	45	19	54	rise
21	47	31	58	rise
14	46	13	38	16

[1]2nd uptake begun on fourth day of hormone administration.

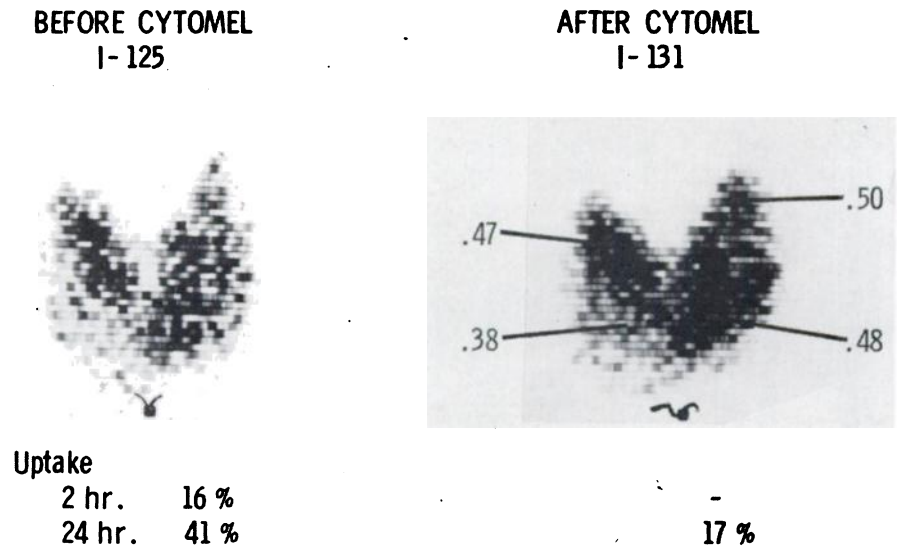

Fig. 1. (Y.K.) Diffuse non-toxic goiter with non-uniform iodine deposition and uniform suppression by T-3. Maximum point-count ratio ($^{131}I \div {}^{125}I$) was 1.2 × average for gland.

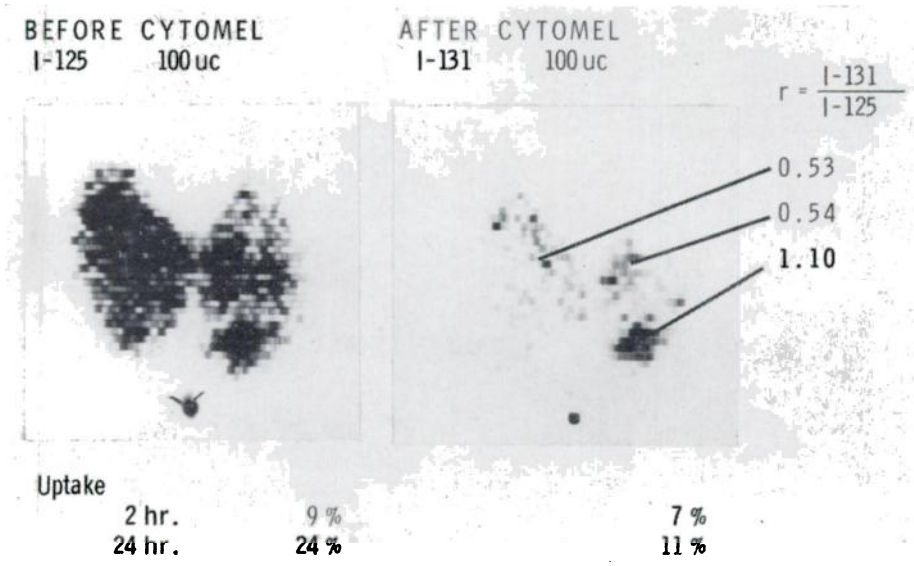

Fig. 2. (M.G.) Diffuse non-toxic goiter with non-uniform iodine deposition demonstrating area of poor suppression in left lower pole. Point-count ratio here was 2.1 × gland average, indicating that differences in the scans are not technical artifacts.

Diffuse Non-Toxic Goiter

Twenty-five euthyroid patients were evaluated and uniform suppression was found in 19 (Table I and Fig. 1). In six of these 19 patients, $^{131}I/^{125}I$ point-count ratios confirmed the visual impression of uniform suppressibility (maximum ratio less than 1.3 × average ratio).

Five euthyroid patients with simple goiter, had localized areas of non-suppression or poor suppression (Table VI and Fig. 2), and in one patient the entire gland was non-suppressible. In three of these six patients the overall uptake fell considerably and the poorly suppressible areas were found only by means of the repeat scan. In two of these patients point-count ratios confirmed the scintigram impression; the ratio over the poorly suppressible area was > 1.7 × that over the remainder of the gland (2.0, 2.1). These patients did not receive TSH.

NODULAR GOITER

Suppressible Warm Nodules

In 8 of 14 patients with functioning ("warm") nodules, the nodules were suppressed to the same degree as the normal extranodular tissue (Table I and Fig. 3). In seven of these eight cases point-count ratios confirmed the scintigram impression (maximum ratio less than 1.3 × average ratio).

Non-Suppressible Warm Nodules

Six of the 14 functioning nodules were either non-suppressible or poorly suppressible, in all cases confirmed by point-count ratios (1.7-7.4 × average) (Table VI and Fig. 4). The overall percentage fall in uptake, 57%, was not significantly different from the suppressible group, indicating that the diagnosis of non-suppressibility must be made both by means of a repeat scan and uptake and not by the uptake alone. All patients in this group were euthyroid.

Hot Nodules[1] *(Table VI)*

Patients were included in this group if (a) subsequent TSH stimulation test revealed the presence of suppressed tissue (23 patients), or (b) because of classical scintigram findings and lack of suppression of the nodule by T-3 (3 cases). One of these 3 latter cases was confirmed as toxic nodular goiter by histopathologic examination (Fig. 5). Of the 26 patients, the 24 hour uptake rose after administration of T-3 in 18, was unchanged in 2 and fell in 6 (5, 7, 12, 15, and 32% of the initial value). Repeat 2 hour uptakes were performed in 21 cases; the values rose in 19, did not change in one, and fell in one. The initial radioiodine uptake study was within the normal range in 20 of the 26 patients and was below the normal range in two.

[1]A hot nodule collects more radioiodine than surrounding thyroid tissue and is autonomous with regard to thyrotropin (34).

In this group of 26 patients a wide spectrum of extranodular autonomy was found, ranging from the classical single hot nodule with no extra-nodular tissue visible (seven cases—27% of total), through multiple hot nodules (4 cases) and hot nodules associated with little to considerable extranodular iodine (18 cases—69% of cases) to generalized toxic nodular goiter (Plummer's disease: one case—Fig. 6). In these latter cases, the extranodular tissue was always as nonsuppressible as the hot nodule and was widely distributed throughout the gland (Fig. 7). In one patient the extranodular tissue was of equal avidity to the nodule for radioiodine, so that the scan suggested asymmetrical Graves' disease (Fig. 5). However, histopathological examination in this case revealed multiple follicular adenomata indistinguishable from other autonomous nodules in this series and different from the findings in diffuse toxic goiter, as well as suppressed tissue.

In six patients of the 118 in this series a final clinical diagnosis was not reached. These patients are not included in the tables.

TABLE IV

EFFECT OF *l*-TRIIODOTHYRONINE ON THYROID UPTAKE OF PATIENTS WITH TREATED DIFFUSE TOXIC GOITER[1]

Method of treatment	*Initial 2 hr*	*Uptake 24 hr*	*Post-T3 2 hr*	*Uptake 24 hr*	*% fall in 24 hr uptake*
I-131	9	15	13	25	rise
I-131	8	21	—	29	rise
I-131	22	47	10	24	50
I-131	15	27	—	34	rise
I-131	4	12	2	4	68
Operation	5	20	7	20	0
Operation	9	26	—	32	rise
Operation	9	27	4	10	64
Operation	4	8	5	12	rise
Drug	4	24	11	38	rise

[1]2nd uptake begun on fourth day of hormone administration.

TABLE V

EFFECT OF *l*-TRIIODOTHYRONINE ON THYROID UPTAKE OF EUTHYROID PATIENTS WITH INFILTRATIVE OPHTHALMOPATHY[1]

Case	*Initial 2 hr*	*Uptake 24 hr*	*Post-T3 2 hr*	*Uptake 24 hr*	*% fall in 24 hr uptake*
1	8	25	8	22	8
2	11	20	—	22	rise
3	12	32	7	20	38
4	13	32	15	47	rise

[1]2nd uptake begun on fourth day of hormone administration.

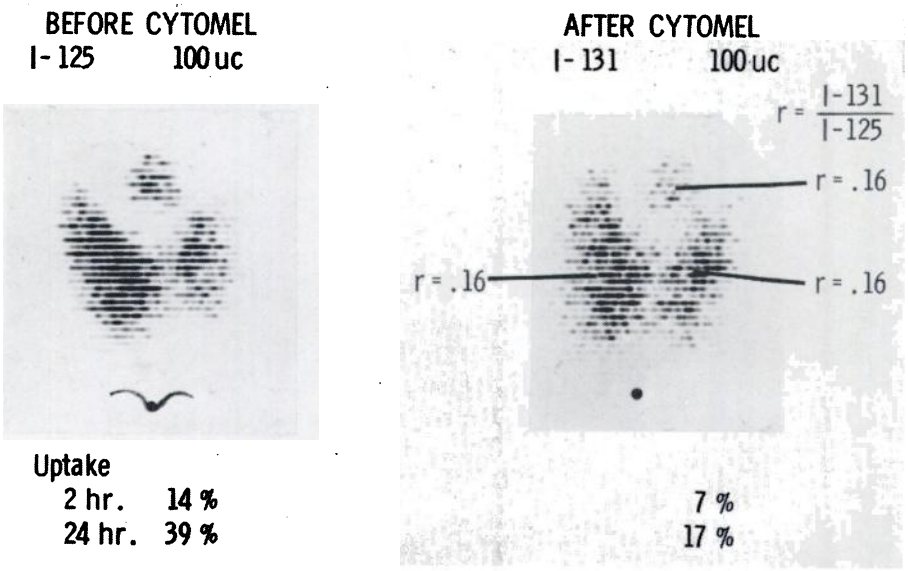

Fig. 3. (I.B.) Functioning nodule in an otherwise normal thyroid gland, showing suppression of nodule equal to normal tissue. Nodule proved to be a benign follicular adenoma of pyramidal lobe.

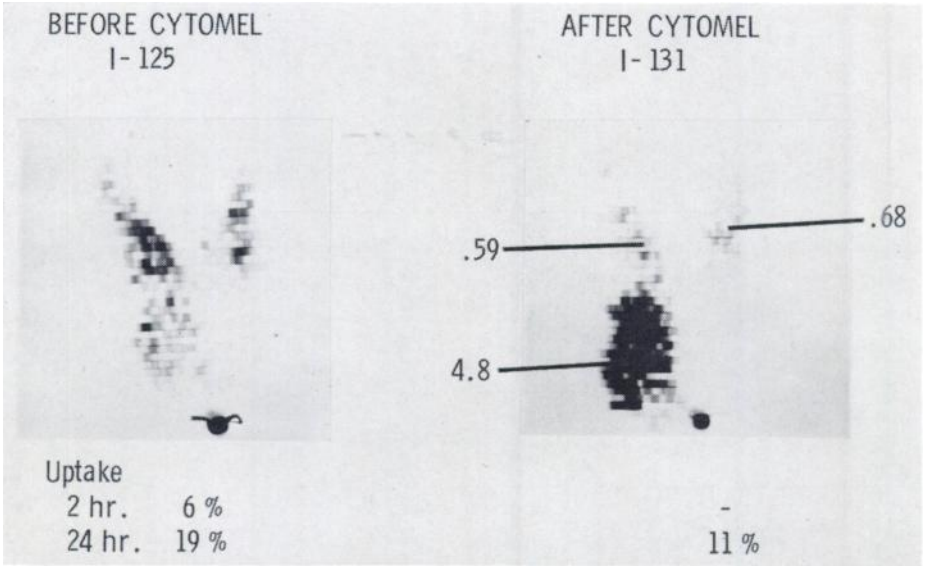

Fig. 4. (M.T.) Poorly suppressible functioning nodule of right lobe in an otherwise normal gland. Point-count ratio over nodule ($^{131}I \div {}^{125}I$) was 7.4 × gland average.

DISCUSSION

Our results demonstrate that the three-day T-3 suppression test is a valid clinical tool which effectively separates hyperthyroid patients with diffuse or nodular goiter from normal normals and patients with suppressible non-toxic goiter. When used in conjunction with the scintigram and two iodine isotopes, the test can detect autonomous thyroid tissue present in both nodular and diffuse goiter, even in euthyroid persons.

In no patient with diffuse toxic goiter was the fall in the 24-hour radioiodine uptake greater than 16%, whereas the smallest fall in the suppressible "euthyroid control" group was 28%. In only one of 26 patients with hot nodules was the fall in uptake greater than 15%.

The mean fall in 24-hour uptakes, in the "euthyroid control" group, 59.5%, was less than the mean fall in a similar group of nine euthyroid patients to whom we gave T-3 or seven to nine days (81%), or in hypophysectomized humans (22). The published data on the T-3 test show that the uptake begins to fall on the second post-treatment day, with a plateau reached on day 5. Thus, although the degree of suppression at three days is not maximal, it is sufficient to completely separate autonomous from suppressible glands.

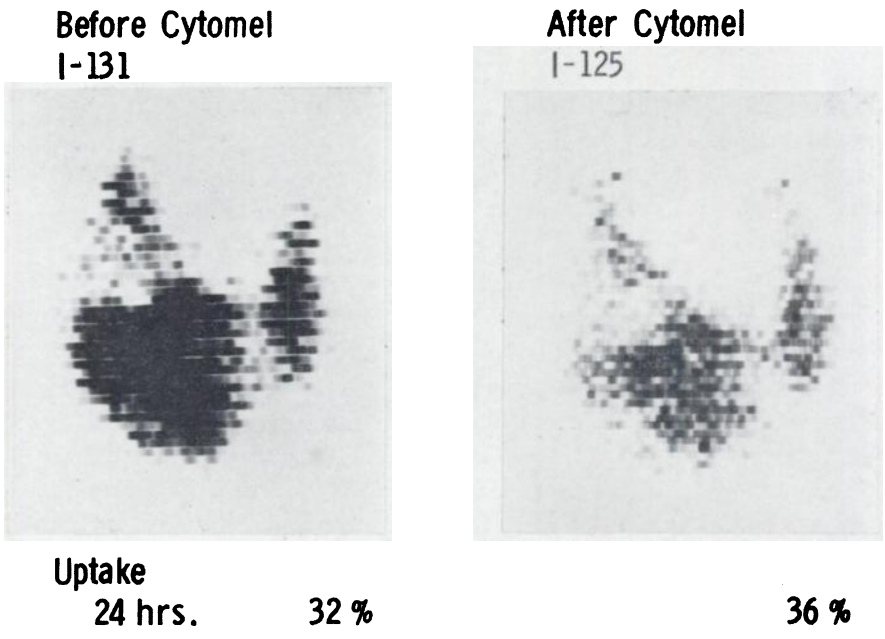

Fig. 5. (A.G.) 65-year-old male with hyperthyroidism. Right lobe was 3-fold enlarged, left lobe 1½-fold, suggesting asymmetrical Graves' disease. Subtotal thyroidectomy revealed follicular adenoma of right lobe (hot nodule) and multiple follicular adenomata of left, as well as suppressed normal tissue.

There is reason to believe that a minimum effective dose of T-3 exists which can deplete the pituitary of its TSH stores. Starr and Liebhold-Schueck (23) found that although 4.4 mcg of T-3 per day had no effect on the uptake, 8.8 mcg produced a maximum drop, not exceeded by even 140 mcg/day. McConahey and Owen, however, found the effect of less than 25 mcg per day to be inconsistent (3). Greater doses did not produce a greater decline in the uptake, but the nadir was reached earlier. Werner and Spooner (1) and Perlmutter and Slater (2) found no difference between the effectiveness of 35 and 75 mcg of T-3 daily.

Although the T-3 suppression test has been uniformly based upon comparison of 24 hour uptakes, we found that in 28 of 29 "euthyroid control" patients the two hour uptake also fell. Other investigators have reported similar results with early uptake determinations (4, 12, 14, 15, 24). This early uptake was of considerable aid in differentiating patients with suppressible glands from those with hot nodules who showed a decline in the 24-hour uptake (five cases of 26). In the latter cases there was a rise or no change in the two hour uptake, whereas in patients with suppressible glands the two hour uptake almost always fell. Sheline and McCormack described a euthyroid patient with a hot nodule whose 24-hour uptake fell from 38 to 29%, but whose 1 hour uptake rose from 7 to 8% (25). Thus, reliance upon the 24-hour uptakes alone, without an early uptake in patients with suspected toxic nodular goiter, could lead to an erroneous diagnosis.

In evaluating criteria for response to the suppression test, the percentage fall in uptake is probably of greater value than the absolute figure finally attained. Thus 98% of our "euthyroid control" patients, with initial 24 hour uptakes of 16% or more, suppressed by more than 30% of baseline uptake (comparable figures of 95% (2) and 93% (13) have been reported). However, three of these 46 "controls" had final uptakes of more than 20%, the cutoff figure suggested by Werner (1). By all other criteria, these three patients had suppressible glands. Furthermore, a number of patients had initial 24-hour uptakes below 21%; this was common among patients with hot nodules (12/26). In such cases, the use of an absolute final value such as 20% has little meaning. Finally, variation in uptake methodology from one laboratory to another may produce considerable variation in absolute uptake values, rendering comparison with published "standards" misleading.

Our results support the contention of Miller (26) that autonomous nodular goiter represents a wide spectrum of functional activities with a similar, if not identical pathogenesis. Thus, we have demonstrated occult autonomy in euthyroid persons with simple goiter (Fig. 2) and in functioning (warm) nodules (Fig. 4) (26-28); in other patients we found multiple autonomous nodules (four cases) (27, 29-32) and generalized autonomy (Fig. 5-7), in addition to the single, classical hot nodule. Our data also supports the thesis of Cope and associates that as more hormone is produced by the nodule (or as it becomes more autonomous) extranodular tissue is suppressed and if enough hormone is produced, hyperthyroidism ensues (29).

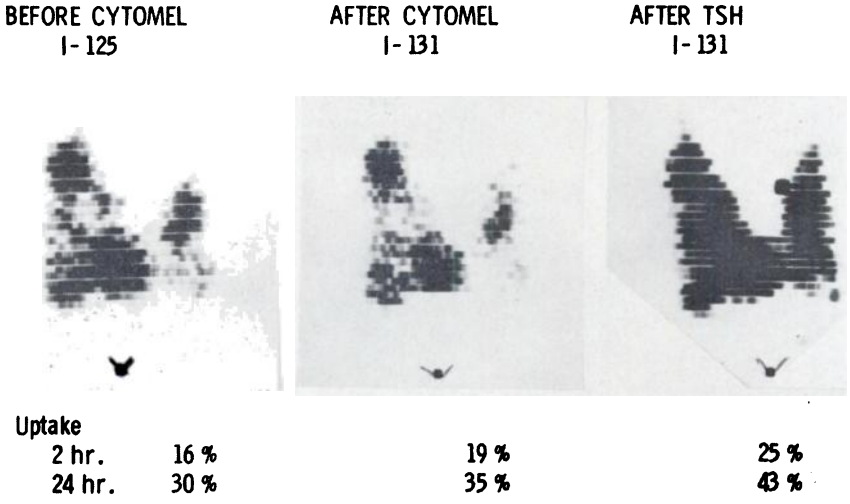

Fig. 6. (A.V.) 44-year-old hyperthyroid female with diffusely enlarged, lumpy thyroid, demonstrating widespread autonomy and stimulation of suppressed tissue by TSH (Plummer's disease).

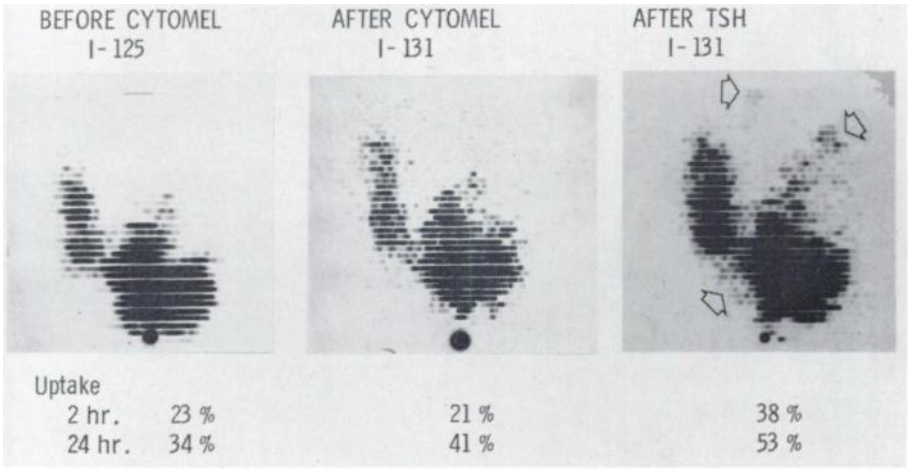

Fig. 7. (F.F.) Hyperthyroid 45-year-old female, demonstrating hot nodule of left lobe and extensive extranodular autonomous tissue. In addition, suppressed normal tissue could be seen after TSH stimulation (arrows). Following ^{131}I therapy, function of this suppressed tissue returned to normal.

In patients with hot nodules, complete absence of extra-nodular function, either on the initial scan or following T-3 administration, was the exception rather than the rule (seven of 26 cases). Our ability to visualize extra-nodular tissue in 19 of 26 patients was considerably higher than the percentages reported by others (31-33), but is in agreement with the data of Sheline and McCormack (25). This is probably attributable to advances in instrumentation, rather than to differences between patient groups. Although this extra-nodular tissue is nonsuppressible, it can usually be stimulated by TSH, a property which differentiates it from truly autonomous tissue (34). It appears that in most cases the extra-nodular tissue is, therefore, suppressed normal tissue and reflects the ability of the thyroid gland to trap and utilize iodine in the absence of TSH.

In view of the frequency of multiple hot nodules and of widespread autonomy, however, the possibility that some of the extranodular tissue is autonomous must always be considered. Thus in patient F. F. (Fig. 7), the visualized extra-nodular tissue is autonomous and suppressed normal tissue is seen only after TSH stimulation. Since the presence of suppressed tissue is a *sine qua non* for the diagnosis of toxic nodular goiter (26), a TSH stimulation test should always follow a T-3 test, which demonstrates both localized and generalized non-suppressibility.

Although occult autonomy was found frequently in both diffuse non-toxic goiter (6/25 patients) and in functioning single nodules (6/14), the patients were not randomly selected for study and these figures are, therefore, not necessarily representative of these disorders as a whole. Our observations, however, corroborate Miller's statement that "in patients without thyrotoxicosis some otherwise nonsuspicious solitary nodules are autonomous and multinodular goiters often have similar areas" (35). These findings may explain occasional reports concerning the failue of patients with diffuse and nodular non-toxic goiter to suppress with T-3, when routine scintigrams were not done as a part of the test (1, 11, 13, 14, 15).

The external point count ratio was of aid in evaluating scans made by different techniques, as well as in identifying suspicious areas of thyroid autonomy, in non-toxic goiter. Figure two shows an area of localized thyroid autonomy, identified by point counting, which might otherwise have been attributed to variation in technique.

The point-count ratio was studied by an approximation method, because not all of the errors in the test were quantitated. The $^{131}I/^{125}I$ ratio tends to be increased by (1) residual ^{131}I from the initial uptake; (2) ^{126}I contaminating the ^{125}I; (3) tissue absorption of the soft ^{125}I x-rays; (4) scatter of higher energy ^{131}I photons (12% of total) into the 364 KeV window; and decreased by (5) ^{131}I scatter into the ^{125}I window. Factors (1) through (4) were not routinely measured. Assuming a biological half-life in autonomous tissue of 46 days (half-normal), it can be shown that the principal sources of error in the ratio are those due to the effective half-lives of the two isotopes and to statistical variation. Factors (1), (2) and (5) amount to less than 6% of the counts and tend to cancel each other out. With the three-day test, the ratio of the effective half-lives is 0.97. Thus, for clinical purposes, the uncorrected ratio of the net $^{131}I:^{125}I$ counts provides a close approximation to the true value. Variations in effective half-life,

TABLE VI

EFFECT OF *l*-TRIIODOTHYRONINE ON THYROID UPTAKE IN PATIENTS WITH AREAS OF POOR SUPPRESSION OR NON-SUPPRESSION ON SCINTIGRAM[1]

Diagnosis	*Clinical status*	*Initial Uptake* 2 hr.	24 hr.	*Final Uptake* 2 hr.	24 hr.	*% fall in 24 hr. uptake*
Diffuse Non-toxic Goiter	Euthy.	9	24	7	11	54
	Euthy.	4	9	5	11	rise
	Euthy.	7	17	—	11	39
	Euthy.	10	25	5	8	70
	Euthy.	18	43	25	51	rise
	Euthy.	5	11	—	14	rise
Functioning Nodule	Euthy.	7	25	—	9	62
	Euthy.	8	20	6	10	49
	Euthy.	13	35	9	9	75
	Euthy.	3	19	—	11	58
	Euthy.	12	22	5	11	52
	Euthy.	6	19	—	11	41
"Hot" Nodule	Hyper.	18	41	38	55	rise
	Euthy.	11	21	18	18	15
	Hyper.	14	27	16	36	rise
	Hyper.	12	26	21	45	rise
	Hyper.	23	34	21	41	rise
	Euthy.	9	23	8	22	5
	Hyper.	5	19	9	24	rise
	Euthy.	12	28	17	33	rise
	Euthy.	18	45	19	42	7
	Hyper.	—	32	—	36	rise
	Hyper.	16	25	18	28	rise
	Hyper.	16	28	30	36	rise
	Euthy.	19	43	—	38	12
	Euthy.	9	19	—	22	rise
	Euthy.	6	9	8	13	rise
	Euthy.	6	8	9	19	rise
	Euthy.	3	18	11	18	0
	Euthy.	6	19	11	26	rise
	Euthy.	11	21	—	17	21
	Euthy.	9	20	9	23	rise
	Hyper.	5	14	7	16	rise
	Hyper.	9	15	12	16	rise
	Hyper.	16	44	22	25	32
	Hyper.	6	17	8	27	rise
	Euthy.	20	23	—	23	0
Multi-Nodular Toxic Goiter	Hyper.	16	30	19	35	rise

[1]2nd uptake begun on fourth day of hormone administration.

however, especially if the test is prolonged for more than one week, may alter the ratio further. The ratio within a suppressible gland was always less than 1.3:1, for any given area counted; that is, no area varied more than 30% from the mean ratio for that gland. In patients with non-suppressible warm nodules, or in autonomous areas in diffuse goiter, the ratio exceeded 1.7:1 (range 1.7-7.4).

Certain conclusions concerning the radioiodine uptake and scan may be drawn from these data:

(1) The radioiodine uptake in hyperthyroid patients with toxic nodular goiter ("hot nodule") is usually normal (11 of 13 patients) (32, 33). Inasmuch as a hot nodule may exist in a gland which is otherwise abnormal (multinodular or diffusely enlarged), it follows that in a patient with a multinodular or diffuse goiter and suspected hyperthyroidism, a normal radioiodine uptake by itself does not rule out thyrotoxicosis. A scintigram must also be obtained and a T-3 suppression test may be necessary.

(2) In euthyroid patients with occult autonomy, in both diffuse and nodular goiter, the diagnosis of localized non- or poor-suppressibility by means of hormone feeding can be made only by both a repeat uptake and scan, since the fall in the overall uptake alone, after T-3, in such patients is usually marked.

(3) In euthyroid patients with overt autonomy (hot nodule on scan), the radioiodine uptake is usually normal or low (11 of 13 patients).

(4) In occasional patients with hot nodules, there may be a fall in the 24-hour radioiodine uptake after T-3 (five of 26 cases). However, in all such patients in this series, the two-hour uptake rose or did not change. This rapid turnover of radioiodine was not seen in normally suppressible glands. Therefore, it is necessary to perform an early uptake, as well as the 24-hour uptake, in conducting the T-3 suppression test. This phenomenon may explain reports in the literature of patients with toxic nodular goiter whose 24-hour uptakes suppressed after hormone administration (32), since in these cases, early uptakes were not routinely done.

SUMMARY

A three-day test of thyroid autonomy has been described, utilizing l-triiodothyronine and two isotopes of iodine (^{131}I and ^{125}I). The test separates patients with hyperthyroidism, due to autonomy from euthyroid patients with suppressible glands.

In 98% of euthyroid patients with suppressible glands, the 24-hour uptake fell by more than 30% from baseline values (16% or greater). In one of 12 patients with diffuse toxic goiter and only one of 26 patients with toxic nodular goiter was the fall in the 24-hour uptake greater than 30%.

Occult autonomy in diffuse or nodular goiters was detected by means of the post-T-3 scan. The overall fall in radioiodine uptake in these patients was no different from the suppressible control group. By means of the isotopic count ratio obtained through a focusing collimator, localized areas of autonomy were identified and studied.

An early uptake determination was found necessary to avoid misinterpreta-

tion of rapid iodine turnover (fall in 24-hour uptake), after T-3 administration, in some patients with overt autonomy.

In patients with hot nodules, whether euthyroid or hyperthyroid, the initial radioiodine uptake was usually normal (20/26 patients).

Autonomy was found to present a wide spectrum of functional appearances, ranging from an occult area in a diffuse or nodular goiter, discovered only by means of the suppression test, through the single hot nodule (with or without hyperthyroidism), to multiple nodules and generalized autonomy, always with the presence of suppressed tissue (except when occult, and in Graves' disease).

Occult autonomy was found in six of 25 selected patients with diffuse nontoxic goiter and in six of 14 selected functioning ("warm") nodules.

ADDENDUM

Since submission of this manuscript for publication, Burke has reported that administration of T-3 to 18 euthyroid patients with hyperfunctioning nodules resulted in a fall in the 24-hour RAI uptake by more than 50% in 2 cases and by more than 30% in 7 (The Triiodothyronine Suppression Test, *Amer. J. Med.* **42**:600-608, 1967). Early uptake determinations were not reported in this group and we therefore cannot agree with Burke's conclusion that "hot" thyroid nodules with sufficient hyperfunction in the adenoma to cause suppression of function in extra-autonomous tissue may exhibit variable degrees of "TSH-dependence." The results of our study clearly show that the effect of T-3 in these patients is not one of suppression but is more likely a TSH-like action (stimulation), the fall in the 24-hour RAI uptake probably representing accelerated discharge of I-131 from the gland.

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REFERENCES

1. Werner, S. C., and Spooner, M.: A New and Simple Test for Hyperthyroidism Employing l-Triiodothyronine and the Twenty-four-hour I-131 Uptake Method. *Bull. N. Y. Acad. Med.* **31**:137-145, 1955.

2. Perlmuter, M., and Slater, S.: Use of Thyroid Hormone to Differentiate Between Hyperthyroidism and Euthyroidism. *J.A.M.A.* **158**:718-20, July 2, 1955.

3. McConahey, Wm. and Owen, C. A., Jr.: Studies on the Inhibitory Effect of l-Triiodothyronine on Thyroidal I-131 Uptake in Euthyroid Persons and Patients with Exophthalmic Goiter. *J. Clin. Endo. and Metab.* **16**:1480-6, 1956.

4. Derome, Gh., Mahaux, J., Henry, J. A.: L'Epreuve d'Inhibition de la Captation Thyroidienne d'I-131 par la l-Triiodothyronine chez les Hyperthyroidiens et chez les Euthyroidiens. *Ann. Endocr.* **18**:1030-5, 1957.

5. Dresner, S., and Schneeberg, N. G.: Rapid Radioiodine Suppression Test Using Triiodothyronine. *J. Clin. Endo. and Metab.* **18**:797-9, 1958.

6. SPENCER, R. P., HENKELMAN, C. R. AND KING, E. R.: Thyroid Parameters During Triiodothyronine Administration. *Metab.* **7**:119-23, 1958.

7. DECOURT, J. AND MICHARD, J. P.: Epreuves de Freinage de la Thyroide au cours d'Etats Neurotoniques Parabasedowiens et d'Exophthalmies Basedowiennes Apparemment Isolees. *Ann. Endocr.* **21**:533-7, 1960.

8. SHIZUME, K., ISHII, J., MATSUDA, K. AND NAGATAKI, S.: Increase of Thyroidal I-131 Uptake Following Administration of Triiodothyronine in some Patients with Hyperthyroidism. *J. Clin. Endo. and Metab.* **20**:1416-9, 1960.

9. HALES, I. B., MYHILL, J., ODDIE, T. H. AND CROYDON, M.: Quantitative Observations with the Triiodothyronine Suppression Test of Thyroid Function. *J. Clin. Endo. and Metab.* **21**:189-95, 1961.

10. BRAKIER, T., AND MERCHIE, G.: The 3, 5, 3^1 -Triiodothyronine Inhibition Test in Thyroid Pathology. *Ann. Endocrin.* **23**:668-77, 1962.

11. KNORPP, C. T., RENNIE, M. H., FRENKEL, E. P. AND KORST, D. R.: The Clinical Application of Thyroid Stimulation and Suppression Tests. *Am. J. Med. Sci.* **244**:316-20, 1962.

12. ZARA, M. AND BORDE, R.: L'Epreuve Dynamique de Freinage Thyroidien a la Triiodothyronine-Test de Werner. Comparison des resultats obtenus par l'emploi du derive racemique et du derive levogyre. Possibilite d'une epreuve raccourcie. *Rev. Franc. d'Endocrin. Clin.* **3**:435-50, 1962.

13. FRIIS, T.: On the Effect of l-Triiodothyronine on the Thyroid Gland and its Clinical Application (the Triiodothyronine Suppression Test). *Acta Med. Scand.* **173**:569-87, 1963.

14. GUINET, P. AND DESCOUR, C.: Le Test de Warner. Experience personnelle. *Gaz. Med. Franc.* **70**:421-33, 1963.

15. KRISTENSEN, H. P. O., DYRBYE, M. AND CHRISTENSEN, L. K.: The Triiodothyronine Suppression Test. *Acta Med. Scand.* **173**:411-22, 1963.

16. VILLELA PEDRAS, J. A., PENNA FRANCA, E. AND PENNA FRANCA, H.: Our Experience with the Suppression Test in the Diagnosis of Thyroid Dysfunctions 415 Tests). *Nucl. Mediz.* **3**:263-71, 1963.

17. AUGER, P., et al: Test de Suppression Thyroidienne. *Canad. M.A.J.* **93**:962-5, 1965.

18. BAKEE, J. L., KAMMER, H., AND LAWRENCE, N.: Effect of Thyroid Hormone on Human Pituitary Thyroid-Stimulating Hormone Content. *J. Clin. Endo. and Metab.* **24**:281-4, 1964.

19. CHARKES, N. D., AND SKLAROFF, D. M.: The Use of Iodine-125 for Thyroid Scintiscanning. *Am. J. Roentgenol.* **90**:1052-8, 1963.

20. LEVY, L. M., ESTRELLADO, T. T., OKEZIE, O. AND STERN, H. S.: The Use of I-125 in Clinical Nuclear Medicine (abstr.). *J. Nucl. Med.* **3**:183, 1962.

21. CHARKES, N. D. AND SKLAROFF, D. M.: Suppression of Functioning Thyroid Nodules with l-Triiodothyronine (Cytomel(R)), Utilizing I-125 and I-131. *Clin. Res.* **12**:264, 1964.

22. LI, M. C., RALL, J. E., MCLEAN, J. P., LIPSETT, M. B., RAY, B. S., AND PEARSON, O. H.: Thyroid Function Following Hypophysectomy in Man. *J. Clin. Endo. and Metab.* **15**:1228-1238, 1955.

23. STARR, P. AND LIEBHOLD-SCHWECK, R.: A Theory of Thyroid Hormone Action Derived from the Differences in the Effect of Selium-Levo-Thyroxine, Sodium detro-Thyroxine, Triiodothyronine, and Potassium Iodide on the Uptake of Radioactive Iodine by the Thyroid Gland of Normal Human Subjects. *Trans. Assoc. Am. Phys.* **66**:97-113, 1953.

24. ODDIE, T. H., RUNDLE, F. F., THOMAS, I. D., HALES, I. AND CATT, B.: Quantitative Observations with the Thyroxine Suppression Test of Thyroid Function. *J. Clin. Endo. and Metab.* **20**:1646-1657, 1960.

25. SHELINE, G. E. AND MCCORMACK, K.: Solitary Hyperfunctioning Thyroid Nodules. *J. Clin. Endo. and Metab.* **20**:1401-1410, 1960.

26. MILLER, J. M., HORN, R. C. AND BLOCK, M. A.: The Evolution of Toxic Nodular Goiter. *Arch. Int. Med.* **113**:72-88, 1964.

27. DORTA, T.: L'utilite de la scintigraphie pour le diagnostic des maladies thyroidiennes et quelques considerations sur le metabolisme de l'iode du goitre nodulaire. *Schweiz. med. Wochenschr.* **90**:1344-1347, 1960.

28. GOROWSKI, T. AND CHOMICKI, O.: Diagnosis of Nontoxic "Warm" Thyroid Nodules Independent of TSH. *J. Clin. Endo. and Metab.* **22**:1267-1268.

29. COPE, O., RAWSON, R., AND MCARTHUR, J. W.: The Hyperfunctioning Single Adenoma of the Thyroid. *Surg. Gynec. & Obstet.* **84**:415-426, 1947.

30. DOBYNS, B. M. AND LENNON, B.: A Study of the Histopathology and Physiologic Function of Thyroid Tumors, Using Radioactive Iodine and Radioautography. *J. Clin. Endo. and Metab.* **8**:732-748, 1948.

31. SAVOIE, J. C.: Etude Clinique et Biologique de Quarante-Trosis Cas d'Adenome Toxique Thyroidien. *Rev. Franc. d'Etudes Clin. et Biol.* **6**:263-275, 1961.

32. MOLNAR, G. D., WILBER, R. D., LEE, R. E., WOOLNER, L. B. AND KEATING, F. R.: On the Hyperfunctioning Solitary Thyroid Nodule. *Proc. Mayo Clin.* **40**:665-684, 1965.

33. SKILLERN, P. G., MCCULLAGH, E. P., AND CLAMEN, M.: Radioiodine in Diagnosis and Therapy of Hyperthyroidism. *Arch. Int. Med.* **110**:888-897, 1962.

34. CANTOR, R. E. AND CHARKES, N. D.: Response of Hot Thyroid Nodules to Exogenous Thyrotropin (abst.) *J. Nucl. Med.* **7**:370, 1966.

35. MILLER, J. M.: Application of Scintillation Scanning in Thyroid Disease. In: Scintillation Scanning in Clinical Medicine, J. L. Quinn, ed. Philadelphia, W. B. Saunders & Co., 1964, pp. 43-54.