

GRAVES' DISEASE WITH FUNCTIONING NODULES

(MARINE-LENHART SYNDROME)

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In 1911 Marine and Lenhart published their observations on the histopathology and iodine content of the thyroid gland in exophthalmic goiter (Graves' disease) (1). Included were eight patients with fetal and follicular adenomas thought to be incidentally related "and in no sense causal". Subsequently, Marine described three more cases, making a total of 11 (2). In five of the eleven patients the iodine concentration in the nodule was 0-3% of that of the extranodular tissue, but in six it ranged from 12 to 40%. (In the atomic age, the first group would be described as "cold" nodules, the second group as "cool"). Later, Puppel and associates described a patient with exophthalmic goiter in whom the ^{131}I concentration in a "colloid nodule" was approximately 31% that of surrounding tissue (3). Dobyns (4) has also identified functioning nodules in patients with Graves' disease by autoradiography.

Following its description by Marine and Lenhart, the syndrome of exophthalmic goiter with incidental functioning nodule(s) was accepted as a distinct subdivision of Graves' disease, and it is now so classified in the most recent schema of the American Thyroid Association (5). In the absence of exophthalmos or acropathic changes, however, the physical findings of the syndrome may be indistinguishable from those of some patients with autonomous nodular goiter (Plummer's disease) and accurate clinical differentiation is then impossible. For example, in a recent study of "toxic nodular goiter" in Finland, Lamberg and associates found that the serum of 10 patients out of 23 (44%) contained the long-acting thyroid stimulator (LATS); i.e., Graves' disease rather than Plummer's disease had been superimposed upon nodular goiter (6).

Despite the fact that the syndrome of Graves' disease with functioning nodule(s) has been recognized by biochemical, immunological, and autoradio-

graphical means, we have found only two probable examples of typical thyroid scans in the literature (6,7). Another case may have been recognized by Means by directional counting (8). There is no description of how this entity may be differentiated functionally from autonomous nodular goiter and there are no reports of its frequency of occurrence or its radiation sensitivity. In this paper we report on these and other observations in ten patients with this syndrome.

MATERIALS AND METHODS

The population for study was composed of hyperthyroid patients seen in our laboratory between October 1966 and July 1971 whose thyroid gland contained one or more palpable nodules which were functioning as determined by thyroid scintigram (Table 1). In all patients a baseline 2- and 24-hr radioiodine uptake and ^{125}I thyroid scan were performed, and subsequent administration of l-triiodothyronine, 25 μg every 8 hr for 3 days, failed to suppress the uptake or to alter the iodine distribution on repeat ^{131}I scan (9). Patients were excluded from further study if administration of thyroid stimulating hormone (TSH), 10 units I.M., stimulated extranodular tissue, since these patients had autonomous nodular goiter (10,11). In some cases multiple TSH injections were given to be certain of the response. Ten patients satisfied these criteria and are referred to as the study group. In all cases, a previously described protocol for a combined 7-day suppression-stimulation test was followed (12).

Point counts with ^{131}I were taken through a

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TABLE 1. LABORATORY DATA IN STUDY-GROUP PATIENTS

Patient	Age	Sex	PBI ($\mu\text{g}\%$)	T_4 * ($\mu\text{g}\%$)	T_3 Upt. (%)	BMR	Length of nodule (cm)	^{131}I uptake					
								Baseline		After T_3		After TSH	
								2	24	2	24	2	24
SL	78	F	11.1	—	—	—	4.5	7	27	7	27	—	46
IM	68	F	—	13.0	—	—	5.0	10	36	10	41	41	70
EW	76	F	12.5	—	—	—	5.5	10	26	10	31	47	62
SL	74	F	12.5	—	39	—	4.0	46	72	40	51	33	53
ME†	57	F	—	—	—	+35	2.5	3	7	2	5	3	7
RS‡	49	F	12.8	—	—	—	4.0	7	23	5	19	32	37
JD	58	F	6.8	—	—	—	7.0	5	26	4	22	27	83
HS	66	M	14.1	—	—	—	7.0	47	68	48	47	58	72
WL	58	F	—	14.3	—	—	6.0	7	25	8	27	17	44
MB	39	F	—	—	36	—	4.5	7	19	7	15	19	43

* Normal 4–11 (Murphy-Pattee).

† Studied 10 yr after ^{131}I therapy; initial ^{131}I uptake 47% at 24 hr.

‡ Studied 2 yr after ^{131}I therapy; initial ^{131}I uptake 63% at 24 hr.

|| Probable T_3 toxicosis; postoperative thyroid storm.

focused collimator over the nodule and extranodular tissue in six patients, prior to and following the TSH injection (11). Exact replacement of the collimator was achieved by superimposing the marked baseline photoscan upon the post-TSH dotscan, with the patient under the probe at the conclusion of the scan study. Iodine-125 autoradiograms were made in one patient by the method of Baserga and with the use of NTB-3 liquid emulsion (13). Unconcentrated serum was assayed in five patients for LATS and antimicrosomal antibody (14) by Kriss.

Comparisons were made with regard to the effect of TSH in 17 consecutive patients with autonomous nodular goiter previously studied by us in an identical manner (11). Overall responsiveness to TSH was also compared with that of 14 patients with diffuse toxic goiter with similar baseline radioiodine uptakes, studied concurrently, and reported in preliminary form (12). All patients were examined by the author.

RESULTS

Response of overall 24-hr radioiodine uptake to TSH. This was compared (Fig. 1) with the responses of 14 patients with Graves' disease without nodules. Neither the baseline uptakes nor the responsiveness to TSH were significantly different between the two groups ($p > 0.1$).

Response of 24-hr radioiodine uptake of the nodule to TSH. Three of six patients studied (Fig. 2) by the point counting technique showed a response to TSH which was greater than that of 17 patients with autonomous nodules. The difference between the mean responses of the two groups was significant at the 0.01 level.

Response of 24-hr radioiodine uptake of the extra-nodular tissue to TSH. The mean response was considerably less in the six study-group patients (2.5-fold increase) than in the 17 patients with autonomous nodules (5.7-fold increase). In the latter

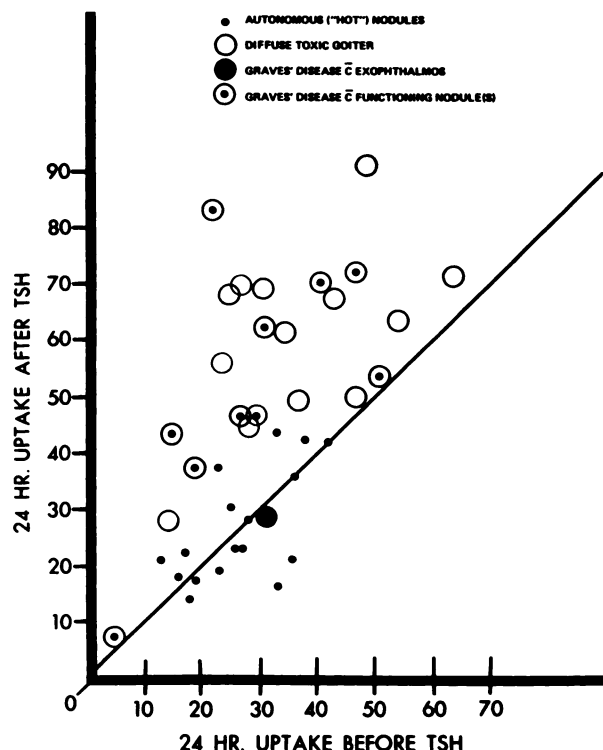


FIG. 1. Twenty-four-hour ^{131}I uptake of entire thyroid gland before (abscissa) and after (ordinate) administration of 10 units of TSH to 14 patients with diffuse toxic goiter and 10 study-group patients ("Graves' disease with functioning nodules"). Responses for 17 patients with autonomous nodules are for nodule alone, not entire gland. Diagonal is line of identity.

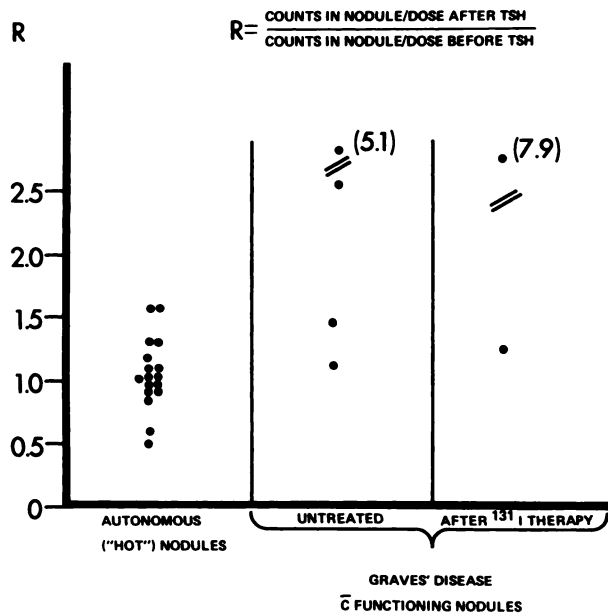


FIG. 2. Response to TSH of nodule, made with focused collimator, in study group and in patients with autonomous nodular goiter. Difference in responsiveness between two groups is significant at 0.01 level.

group, however, the baseline uptake was low whereas in the study group it was normal or elevated.

Response ratio to TSH. This was calculated (Fig. 3) as follows:

$$R = \frac{{}^{131}\text{I uptake of nodule after TSH background} / {}^{131}\text{I uptake of nodule before TSH background}}{{}^{131}\text{I uptake of extranodular tissue before TSH background} / {}^{131}\text{I uptake of extranodular tissue after TSH background}}$$

The mean ratio was clearly different for the six study-group patients and the 17 patients with autonomous nodules ($p = <0.001$). The response ratio of four of the study-group patients was 1.0 or greater, indicating that these nodules were at least as responsive as the extranodular tissue to TSH.

Response to ${}^{131}\text{I}$ therapy. Six patients were treated for hyperthyroidism with ${}^{131}\text{I}$. The total number of millicuries which rendered these patients euthyroid ranged from 5.5 to 17 mCi and was greater than the corresponding mean, median, and mode dose required in 75 patients with Graves' disease without nodules [mean 8.6 as compared with 7.1 mCi ($p = <0.05$); median 7.0 as compared with 6.0 mCi; mode 7.0 as compared with 3.5 mCi, respectively]. When the response was plotted in terms of microcuries deposited per gram* of thyroid tissue (Fig. 4),

* Gland weight was estimated from the photoscan, assuming each lobe and nodule to be a prolate ellipsoid in which depth (z axis) equals width (y axis).

three of six patients were found to have required a radioiodine concentration greater than 85% of those patients without nodules (65 of 75), suggesting a greater radioresistance in some patients with functioning nodules ($p = <0.05$). Sequential scintigrams in three of the six treated patients disclosed a marked change in the relative deposition of iodine after therapy, resulting in a striking prominence of the nodules. The scintigrams of one such patient are shown in Fig. 5. In these three patients the nodule was clearly more radioresistant than the extranodular tissue. Responsiveness to TSH was retained following treatment in both nodule and extranodular tissue in all three of these patients and in two of the three the nodule was more responsive. In the other three patients, following treatment there appeared to be no change in the relative radioiodine distribution on scintigram between nodule and extranodular tissue.

Operative findings. Two of the ten study-group patients underwent thyroidectomy. One of the patients had previously been treated with ${}^{131}\text{I}$ and was

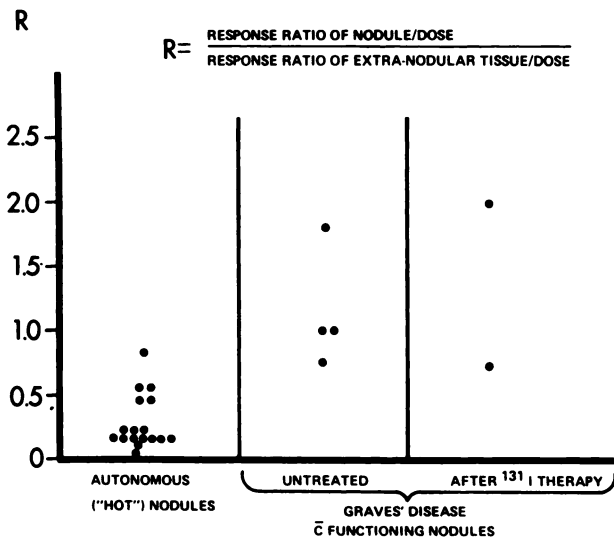


FIG. 3. Response ratio to TSH of both nodule and extranodular tissue. Method of calculation is given in text. Difference between two groups is highly significant ($p < 0.001$).

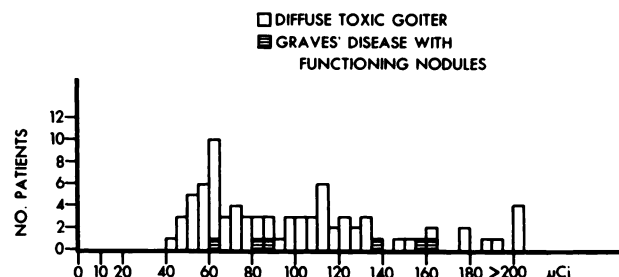


FIG. 4. Dose of ${}^{131}\text{I}$ which relieved hyperthyroidism in 75 patients with diffuse toxic goiter and 6 study-group patients, in terms of microcuries deposited per gram of tissue.

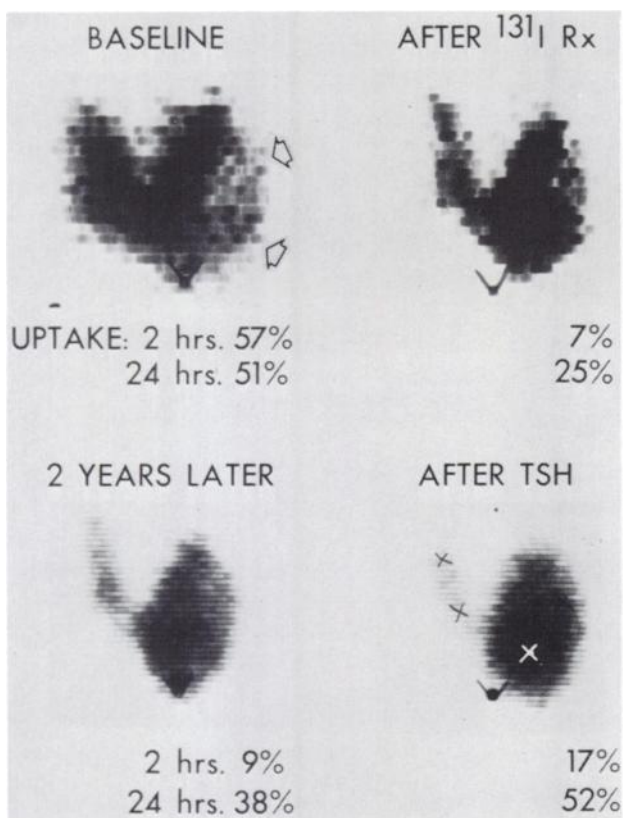


FIG. 5. (A) baseline ^{125}I scan made in Patient WL, 58-year-old hyperthyroid woman. Thyroid gland was threefold enlarged with prominent 6-cm nodule in left lobe (arrows). Note that radioiodine concentration in nodule is less than in remainder of gland and is not distributed uniformly. (B) 3 months after treatment with 7.0 mCi of ^{131}I ; patient was euthyroid. Extranodular tissue is smaller than before therapy, and concentration of radioiodine is less than in nodule. (C) 2 years later there has been further decrease in function of extranodular tissue in comparison with nodule; patient was taking l-thyroxine and uptake was nonsuppressible (D). Note increase in uptake after TSH. Crosses (X) mark sites at which counts were taken with focused collimator.

euthyroid. In this patient the nodule proved to be a follicular adenoma (Figs. 6, 7); nuclear polyploidy was marked in the extranodular tissue but was minimal in the adenoma itself. Widespread degenerative changes (old hemorrhage, edema, fibrosis, and calcification) were seen microscopically in this nodule. In the other patient the pathologic diagnosis was adenomatous hyperplasia, and an autoradiogram in this case confirmed the ability of the nodules to trap iodine.

Frequency of occurrence. During the 58-month period of October 1966 through July 1971, 375 patients with Graves' disease were referred to our nuclear medicine section for radioiodine testing. All patients had a radioiodine uptake and scan, and Plummer's disease was excluded by TSH testing as described above (10,11). The distribution of cases, based upon physical and scintigraphic findings, is

given in Table 2. Graves' disease with functioning nodules occurred in ten patients (2.7%).

Scintigraphic appearance. In nine of the patients in the study group a single nodule was present, measuring 2.5 to 7.0 cm in the greatest diameter on scan. One patient had multiple nodules. In almost all of the patients (9/10) the nodule appeared to concentrate somewhat less radioiodine than the remainder of the gland, and would be described by some as "cool" (Figs. 5, 6). A typical scintiscan study is illustrated in Fig. 8. In one patient, the iodine concentration in the nodule was similar to that in the remainder of the gland (Fig. 9). In nine of the ten patients the iodine deposition within the nodule was irregular, suggesting degenerative changes (Figs. 5, 6, 8, 9). In all cases TSH failed to stimulate any suppressed tissue (this was a criterion for selection), although the uptake of the gland (nodule and extranodular tissue) rose in nine patients

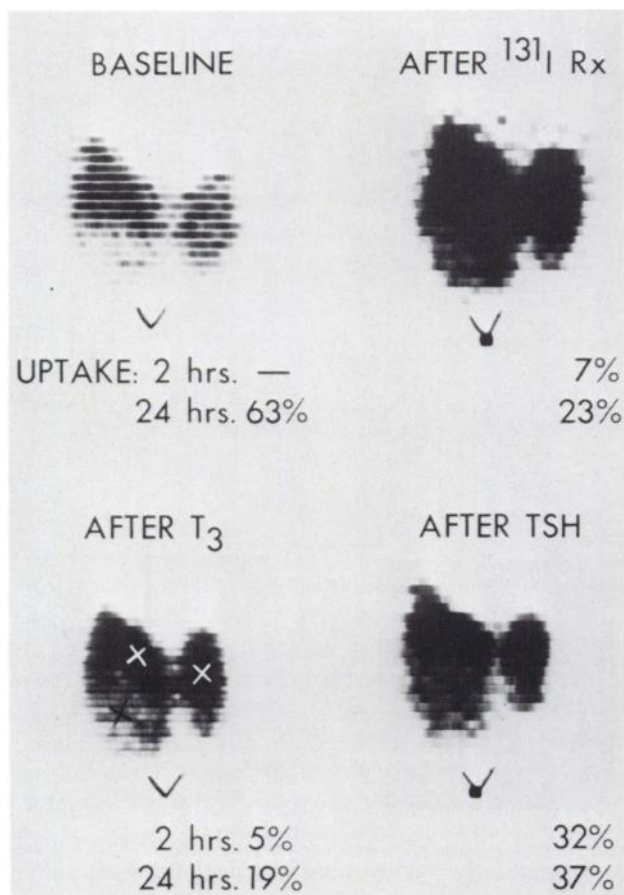


FIG. 6. (A) thyroid scan shows functioning nodule in right lower pole. Iodine concentration is less than that of extranodular tissue, and its distribution is not uniform. (B) 2 years after successful radioiodine therapy (6.5 mCi ^{131}I) relative distribution of ^{125}I in gland is changed, with relatively greater uptake now in nodule. (C) after l-T₃ there is no change in radioiodine uptake or distribution. Crosses mark counting sites. (D) After TSH there is marked increase in radioiodine uptake. Counting rate over nodule rose 196% higher than over extranodular tissue. Following these studies nodule was excised.

FIG. 7. Same patient as in Fig. 6. Microscopic sections revealed follicular adenoma. (A) low power view shows separation of follicles by edema and fibrous tissue (arrows). c is capsule, e is extranodular (normal) tissue. Hematoxylin and eosin (H&E), $\times 21$. (B) higher magnification shows large, polyploid nuclei in extranodular tissue (arrows). There are nine such nuclei in this field. H & E $\times 400$. (C) view of adenoma, same magnification as in (B), showing only one polyploid nucleus in field (arrow). This is consistent with greater degree of radiation damage to extranodular tissue than to adenoma.

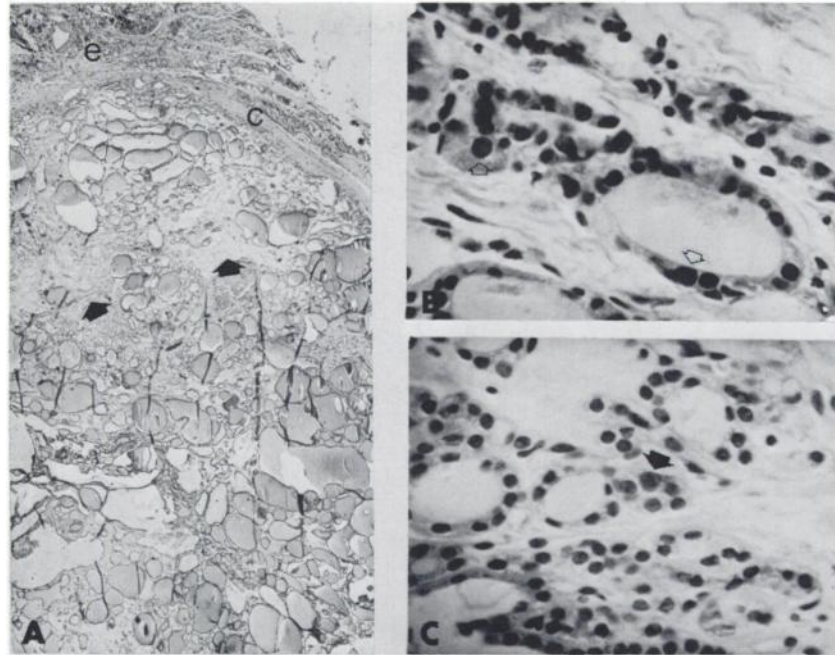


TABLE 2. CLASSIFICATION OF 375 PATIENTS WITH GRAVES' DISEASE, OCT. 1966-JULY 1971

Form	No. of patients	Total (%)
Diffuse toxic goiter	333	88.8
With colloid goiter	20	5.3
With cold nodule	12	3.2
With functioning nodule	10	2.7
Total	375	100.0

(Fig. 1); representative responses are seen in Figs. 5, 6, 8, and 9.

Serologic studies. Unconcentrated serum was assayed for LATS in five patients and was negative in all. In four of the five, the specimens were drawn 20 months to 5 years following radioiodine therapy, when the patients were euthyroid. Antimicrosomal antibody was present in the sera of all four patients tested, in high titer in two patients (96, 158, 3,500, and $>62,000$ units/ml; normal <10 units/ml). In one patient with Plummer's disease given 75 mCi of sodium iodide ^{131}I (not included in this series) the antimicrosomal antibody titer was less than 100 units/ml and did not change before and following treatment at monthly intervals for 3 months.

DISCUSSION

In 1913, Plummer and Wilson described a previously unrecognized form of hyperthyroidism characterized by its insidious onset, long history of goiter,

absence of exophthalmos, and the presence of areas of "regeneration" or adenoma (15,16). More than three decades later it was shown that the nodules in these cases trapped virtually all administered radioiodine, and the extranodular tissue was functionally atrophic (17,18). Cope and associates postulated that the nodule was hyperfunctioning and its output of thyroid hormone had resulted in anatomic and functional atrophy of the remainder of the gland (17). Subsequently, it was shown that TSH could stimulate the iodine uptake of the extranodular tissue (19) but not the nodule itself (11), i.e., the nodule is autonomous in this disease.

The syndrome described in this paper is clearly the manifestation of a different pathologic process from that described by Plummer. In the first place, the quantitative response to TSH of the nodule in three of six patients tested was markedly greater than that of any of 17 patients with autonomous nodules ($p = 0.01$) (one of the three patients who failed to respond had previously been treated with radioactive iodine). In addition, the extranodular tissue was less responsive to TSH than it was in patients with autonomous nodules. When these data were combined to express the responsiveness to TSH of the nodule and the extranodular tissue ("response ratio"), a significant difference was observed between the study group patients and those with autonomous nodular goiter (Fig. 3; $p < 0.001$).

Secondly, when the overall radioiodine uptake of the thyroid gland was measured, there was no significant difference in responsiveness to TSH between the study-group patients and patients with diffuse

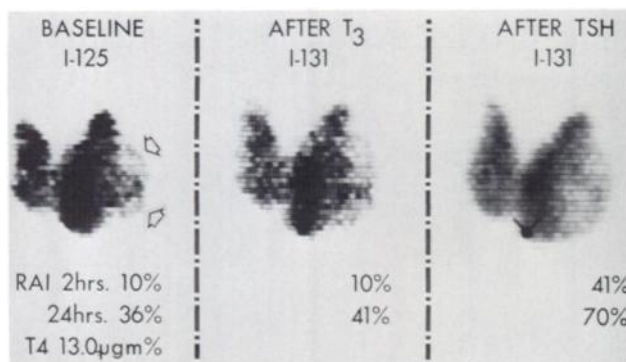


FIG. 8. Typical scintigraphic appearance of functioning nodule (arrows) associated with Graves' disease (Patient IM, 68-year-old woman). Note marked uniform response to TSH on scintigram. Point counts over midportion of nodule showed 1.4-fold response, same as mean response over extranodular areas of gland.

toxic goiter who had similar baseline radioiodine uptakes ($p > 0.1$). This suggests that these two groups were not drawn from different populations.

Thirdly, when the study-group patients were treated with radioactive iodine and became euthyroid or hypothyroid, there was either no change in the distribution of iodine as measured by scintiscanning (Fig. 9), or the uptake of the extranodular tissue became markedly depressed in comparison with that of the nodule (Fig. 5). This is not the response seen in patients with Plummer's disease: autonomous nodules are either ablated completely or their uptake is markedly depressed, but in either case, following radioiodine therapy there is relatively more uptake in the extranodular tissue than in the nodule.

These findings strongly suggest that the ten study-group patients have Graves' disease with incidental functioning nodules, the syndrome described by Marine and Lenhart. Unequivocal exophthalmos, however, was present in only one of them, and LATS was not detectable in the five patients from whom serum samples were obtained. LATS levels, though, tend to decrease with time in some patients and may disappear within a year after ^{131}I treatment (19); four of the five patients were studied 20 months to 5 years following radioiodine therapy. Antimicrosomal antibody was found in the serum of all four patients tested, and was in high titer in two patients. This antibody is not specific for Graves' disease, but has been found in virtually all patients with this disease tested so far (14,20). Its presence in the study-group patients strengthens the probability that they have Graves' disease.

The scintigraphic appearance of the nodule in the study-group patients was not that usually seen in patients with Plummer's disease. In most cases the nodule appeared to concentrate somewhat less radio-

iodine than the remainder of the gland (Figs. 5, 6, 8). This accords with the data of Marine and Lenhart and of Puppel, et al, who found that the iodine concentration of functioning nodules in patients with Graves' disease was 12–40% of that of the extranodular tissue. The reason is found in a study of the architecture of the nodule: in many adenomas the follicles are not closely packed but are separated by an edematous stroma, collagen bundles, areas of hemorrhage, cholesterol clefts, cysts, and other signs of degeneration (21). These changes were found in the adenoma excised in Patient RS (Fig. 7). They are thought to be related to the inadequacy of the vascular supply of the nodule which comes from the capsule (1). Similar degenerative changes are also seen in autonomous and in nonfunctioning nodules (11,18,21).

Six patients in the group were treated with radioiodine. The amount of radioiodine required to relieve the hyperthyroidism was greater than the corresponding mean, median, or mode dose required for patients with diffuse toxic goiter. This appeared to be the result of the large size of these goiters as

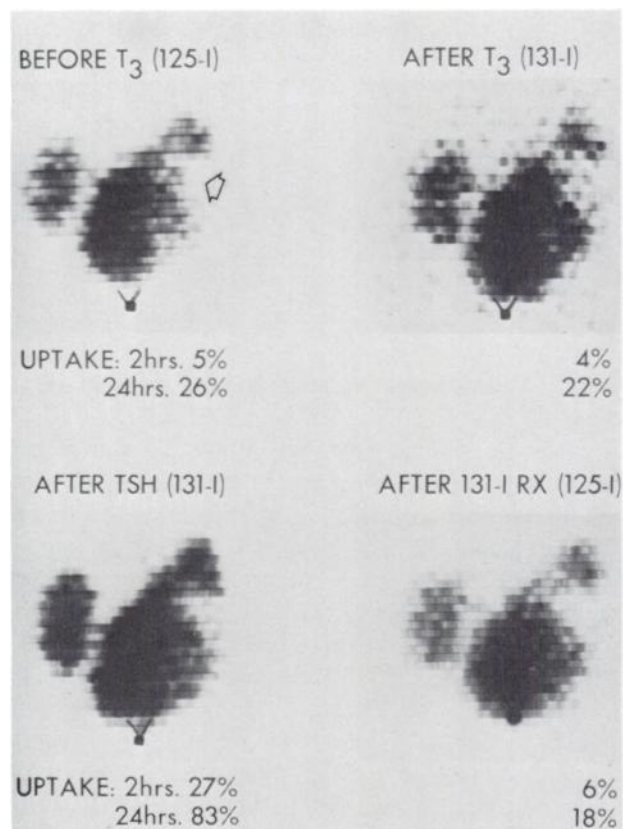


FIG. 9. Scintigrams made in Patient JD, 51-year-old woman with hyperthyroidism. (A) nodule in left lobe measured 7 cm. Note that radioiodine concentration in nodule is equal to that in right lobe. Area of decreased uptake is seen in upper portion of nodule (arrow). (B–D) following successful ^{131}I treatment, relative radioiodine deposition in nodule and extranodular tissue is unchanged, nonsuppressible, and equally responsive to TSH.

well as the relative radioresistance of some of them, since the ^{131}I concentration which was required in three of the six was greater than that needed by 85% of the patients without nodules. Striking examples of the relative radioresistance of some nodules were seen by scintiscanning in three patients (Fig. 5). One of these patients was operated upon one year after successful radioiodine therapy; histopathologic examination revealed a follicular adenoma with marked nuclear polyploidy in the extranodular tissue but only scattered polyploidy in the nuclei of the adenoma. This finding is consistent with greater radiation damage to the extranodular tissue than to the nodule (22). Quantitative measurements made with the focused collimator in this patient following radioiodine therapy revealed considerably greater responsiveness of the nodule than the extranodular tissue to TSH consistent with the histopathologic findings.

These results suggest that some nodules are more resistant to the effects of radioiodine therapy than is the extranodular tissue and the euthyroid state may then depend upon the output of thyroid hormone by the nodule. Since subsequent degenerative changes in the nodule are common, subtotal thyroidectomy may be the treatment of choice in this condition.

When we reviewed our experience during the past 58 months in this hospital, it was found that of 375 patients with Graves' disease referred for radioiodine testing, 10 (the study group) had incidental functioning nodules, a frequency of 2.7%. In 12 other patients (3.2%), Graves' disease was associated with nonfunctioning ("cold") nodules. The completely coincidental nature of the association of Graves' disease with single thyroid nodules has been stressed for many years (1,3,7,8,23). It is interesting to note that in their original report, Marine and Lenhart found functioning nodules (iodine concentration, 12–40% of extranodular tissue) in 3 of 69 patients with Graves' disease (4.3%), a figure not significantly different from the findings reported in this paper. We have been unable to find any other series of Graves' disease patients studied with respect to the function of incidental nodules.

The possible significance of the syndrome is suggested by several reports in which a small but significant proportion of hyperthyroid patients could not be classified by existing diagnostic methods. Cole and Fowler, writing in 1948, stated that "in our experience a definite clinical differentiation between toxic diffuse and toxic nodular goiter cannot be made in about 15 per cent of cases" (24). In a more recent evaluation of approximately 35,000 patients with hyperthyroidism treated by surgery, drugs, or radio-

iodine, a study group of the American Thyroid Association was unable to classify about 4.5% of the patients as having either Graves' or Plummer's disease (25). It is tempting to speculate that many of these patients may have had Graves' disease with functioning nodules.

Finally, it seems appropriate to refer to the entity of Graves' disease with functioning nodules as the Marine-Lenhart syndrome in recognition of the investigators who first identified it. The diagnosis is made by (A) demonstration of nonsuppressibility of radioiodine uptake in a hyperthyroid patient whose thyroid gland contains one or more functioning nodules; (B) failure of TSH to alter the scintigraphic appearance of the thyroid gland; (C) stimulation of overall radioiodine uptake by TSH (Fig. 1) (12); and (D) stimulation of radioiodine uptake by the nodule by TSH, 1.7-fold or greater (Fig. 2). Criteria (A) and (B) must be satisfied in each case to rule out Plummer's disease; the diagnosis can then be made by exclusion. Criterion (C) is applicable when the baseline radioiodine uptake is normal or slightly elevated, but not necessarily when it is markedly elevated (12). Criterion (D) is not valid diagnostically when the TSH response is in the overlap range, 1.1–1.6. In routine practice, neither criterion (C) nor (D) is required for diagnosis but they may be needed in certain situations. For example, it is conceivable that both Graves' disease and Plummer's disease could coexist in the same patient (26); demonstration of a response to TSH by the nodule greater than 1.7-fold would rule out this possibility but a response less than 1.1-fold would make it very likely (Fig. 2).

SUMMARY

Ten hyperthyroid patients with functioning thyroid nodules were studied in whom Plummer's disease (autonomous nodular goiter) had been excluded by failure of TSH to stimulate suppressed extranodular tissue. The responses of the nodules and the extranodular tissue to TSH administration were significantly different from those seen in Plummer's disease and were consistent with the responses noted in patients with Graves' disease. It was concluded that these patients had Graves' disease with incidental functioning nodules. In three of six treated patients, the nodules were relatively resistant to ^{131}I therapy, as judged by dose requirement, post-treatment scintigrams, and measurements of nuclear polyploidy. Subtotal thyroidectomy may therefore be the treatment of choice in this syndrome. The frequency of occurrence of incidental functioning nodules was found to be 2.7% of 375 patients with Graves' disease referred to us for testing. In recognition of the

investigators who first described this entity biochemically, it is proposed that Graves' disease with incidental functioning nodules be called the Marine-Lenhart syndrome.

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