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# Diagnosis and Management of Large Toxic Multinodular Goiters

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Toxic multinodular goiters, estimated weight 100 g or more, occurred in 35 patients between 1961 and 1984. All but two were older than 50; 32 were females. Twenty had goiters of 100–130 g; four of 140–200 g; and 11 were massive. Radioiodine uptakes were 30% or less for 22. Seven of 17 with both  $T_4$  and  $T_3$  data had  $T_4$  toxicosis. Thirty-two patients received radioiodine therapy, delivering 200  $\mu$ Ci per gram when possible. Doses were 25–30 mCi for 17 patients; 50–100 mCi for 12 patients, and 150–200 mCi for three patients. Hyperthyroidism was eliminated with one dose in 25 patients (78%); five patients required two doses. Twenty-two patients were euthyroid after radioiodine; 25 of 28 had persistent goiters. Two patients were treated successfully surgically. One refused surgery and radioiodine, and has been maintained on antithyroid drugs for 10 yr. Two patients died within a few months of an unsuccessful initial dose of radioiodine. Large dose radioiodine therapy is simple, safe, and effective for most patients with large toxic multinodular goiters.

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In 1913, Henry Plummer described important differences in the clinical presentation of the toxic multinodular goiter (TMNG) from that of Graves' disease. Patients with TMNG do not have the typical ophthalmic or acral findings of Graves' disease, but more often have preexisting goiter for many years prior to the onset of hyperthyroidism and are older and more likely to have cardiac complications (1). Recently, it has been shown that patients with TMNG have lower radioactive iodine uptake (RAIU) values (2), and may have less striking elevations in serum thyroid hormone concentrations (3), especially  $T_3$  levels. In our clinic, for every patient with TMNG there are nearly 50 with Graves' disease.

The goiter of TMNG tends to be larger than that of Graves' disease with about half the TMNG patients having goiters of 100 g or larger. Enormous TMNG, although less common than in the past, are still occasionally seen.

The large TMNG, 100 g or larger, may present formidable management problems. These patients are often elderly, and have associated heart failure or rhythm disturbances, features that increase the risks of surgery. The large size, extreme irregularity of func-

tion, and lesser avidity for radioactive iodine renders these large TMNG more radio-resistant than goiters of Graves' disease. Sustained clinical remissions are virtually never achieved using antithyroid drugs.

Although large TMNG are uncommon, physicians must be prepared to deal with them. The current American medical literature is notably silent on the subject, and standard textbooks on thyroidology or endocrinology are not very helpful. Some textbooks advise higher doses of radioactive iodine, but offer no specific dosage information (2,4). Another textbook suggests that surgery would be ideal, if these patients were not such poor operative risks (5).

This report will describe our experiences in the management of 35 patients with large TMNG. Treatment with radioactive iodine will be discussed in terms of methods and results.

## MATERIAL AND METHODS

From the records of 56,676 thyroid patients seen in the author's clinic between 1961 and 1983, 85 patients with TMNG were recovered, 35 of whom had goiters of 100 g or larger. These patients were differentiated from those with Graves' disease on the basis of the absence of ophthalmic or acral signs of Graves' disease, and by the presence of multinodular goiters. Thyroid images showed diffuse tracer uptake, but often patchy and

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**TABLE 1**  
Age and Sex for Patients with Large TMNG

Age (yr)	Sex	
	M	F
<35	0	0
35-49	0	2
50-64	0	7
65-79	3	18
80+	0	5
Total	3	32

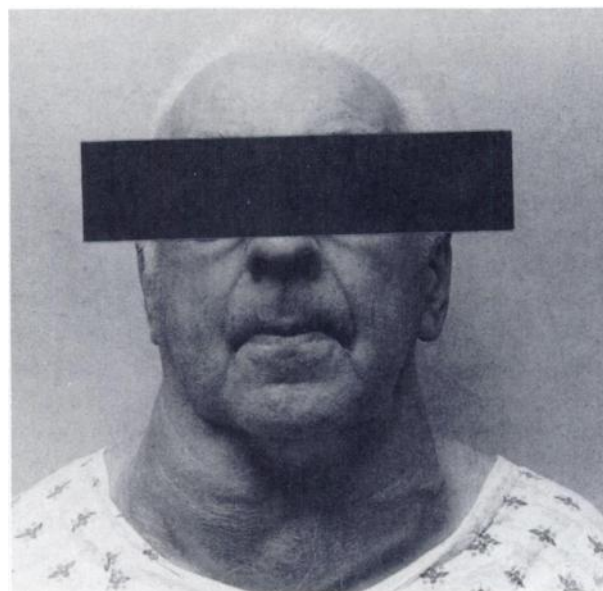
irregular, rather than the uniform pattern of Graves' disease, or the confinement of tracer to a solitary nodule characteristic of the toxic autonomous adenoma. It is possible that some of the patients had Graves' disease superimposed upon a preexisting multinodular goiter. Inability to test for thyroid stimulating immunoglobulins precluded the possibility of assuring absolute homogeneity of the series in this respect. However, the elderly patient with hyperthyroidism of Graves' disease and a large multinodular goiter would present the same therapeutic challenges as one with toxic multinodular goiter.

Diagnoses of hyperthyroidism were established on the basis of clinical findings and supported by in vitro assays of thyroid hormone levels. Over the years, various methods of assay were employed, but at least one elevated in vitro assay was available for each patient. Of the more recent cases, five had TRH testing as well. A baseline specimen for serum TSH assay was obtained, followed by the intravenous injection of 100  $\mu$ g of TRH, and a 20-min post-injection specimen for a repeat TSH assay. A normal response in our laboratory was an increment in the TSH concentration of 2-20  $\mu$ U/ml.

For 14 of the large TMNG patients, large goiters had been present for 20 to 40 years or longer before hyperthyroidism developed. For five additional patients, goiters had been present for 1 to 4 years before the onset of hyperthyroidism. The larger the goiter, the cruder the estimate of weight, whether based on examination (our practice), thyroid imaging, or combinations of methods. Also, any weight estimate would not give any indication of the weight of functioning parenchyma, because these goiters invariably have substantial degenerated components.

**TABLE 2**  
Estimated Goiter Weight for Patients with Large TMNG

Estimated weight (g)	No. patients
100-130	20
140-200	4
>200 (massive)	11
Total	35



**FIGURE 1**  
Typical appearance of patient with massive toxic multinodular goiter

The objective of radioiodine therapy was thyroid ablation to achieve a maximum one-dose cure rate (6). For some cases, this objective was compromised by patient reluctance to be hospitalized for treatment, as required in the United States for patients receiving 30 mCi or more of radioactive iodine. In view of the technical impossibility of making any valid estimate of the weight of functioning thyroid tissue, dosimetry was necessarily empirical. We attempted to deliver 200  $\mu$ Ci per gram of estimated weight of the goiter, without regard to what proportion of the tissue was functional. This led to doses between 20 and 200 mCi.

Of the 35 patients, 18 had associated heart disease, principally atrial fibrillation and congestive heart failure. These problems were controlled with digitalis and diuretics. Seventeen patients were also prepared for radioiodine by a course of antithyroid drugs of 30 to 60 days' duration. The objective of antithyroid drug preparation was to reduce the blood levels of thyroid hormone to upper level of normal or below. Propylthiouracil was the principal drug used, and the usual dose was 300 mg q.i.d. Preparation with antithyroid drugs was employed, not only for patients with associated heart disease, but also for those who were elderly and severely toxic.

Beta blockers were seldom used in these patients because the problem was not the severity of the thyrotoxicosis per se, but concern for worsening of the thyrotoxicosis after radioiodine therapy because of discharge of preformed thyroid hormone that would further elevate already high blood levels of thyroid hormone. This could have a deleterious impact on a marginally compensated or decompensated cardiovascular system.

**TABLE 3**  
Baseline RAIU Values for Patients with Large TMNG

RAIU	No. patients
<21	2
21-30	20
31-40	6
41-50	7
50+	0
Total	35

Stable iodine was not given, and should be avoided in these patients because it may exacerbate the hyperthyroidism (Jod-Basedow phenomenon), even in patients taking antithyroid drugs.

## RESULTS

Table 1 gives the age and sex distribution of the patients. Note that 81% of the patients with large TMNG were 65 or older; and 91% are women. Five patients were first seen prior to 1970, when fewer referrals were received. Between 1970 and 1974, a period of time in which the number of referrals was relatively stable, 13 patients were seen; 12 patients were seen between 1975 and 1979; and six patients were seen between 1980 and 1984.

Table 2 shows the estimated goiter weight. For 11 patients, the goiters were too large for any reasonable weight estimate. Figure 1 shows the appearance of a representative patient with a massive toxic multinodular goiter.

Table 3 gives the baseline RAIU values. Note that 63% of patients with large TMNG had values of 30% or less. In comparison, for 50 consecutive patients with Graves' disease who were older than 50, these lower RAIU values were present only 38% of the time, and for 50 consecutive patients with Graves' disease younger than 50, lower RAIU values were found only 10% of the time. Only one of the five patients who received second doses of radioiodine (two patients refused further study and retreatment) had a RAIU value prior to the second dose that was substantially lower than the baseline RAIU (baseline RAIU 30%, RAIU prior to the second therapy dose 17%). Two patients had higher RAIU values before the second therapy dose.

For 17 of the 35 patients, data for both serum T<sub>3</sub> and T<sub>4</sub> concentrations were available. Table 4 shows that seven patients (41%) had elevated serum T<sub>4</sub> values without elevated serum T<sub>3</sub>. Reduced efficiency of the deiodination of T<sub>4</sub> to T<sub>3</sub> seems to be a feature of aging, and may explain these results. TRH tests were performed on five patients, and all gave blunted results.

Treatment of the large TMNG was radioiodine therapy for 32 of the 35 patients, surgery for two, and long-term antithyroid drug therapy for one. One of the

**TABLE 4**  
Serum T<sub>4</sub> and T<sub>3</sub> Levels in Patients with Large TMNG when both Assays were Performed

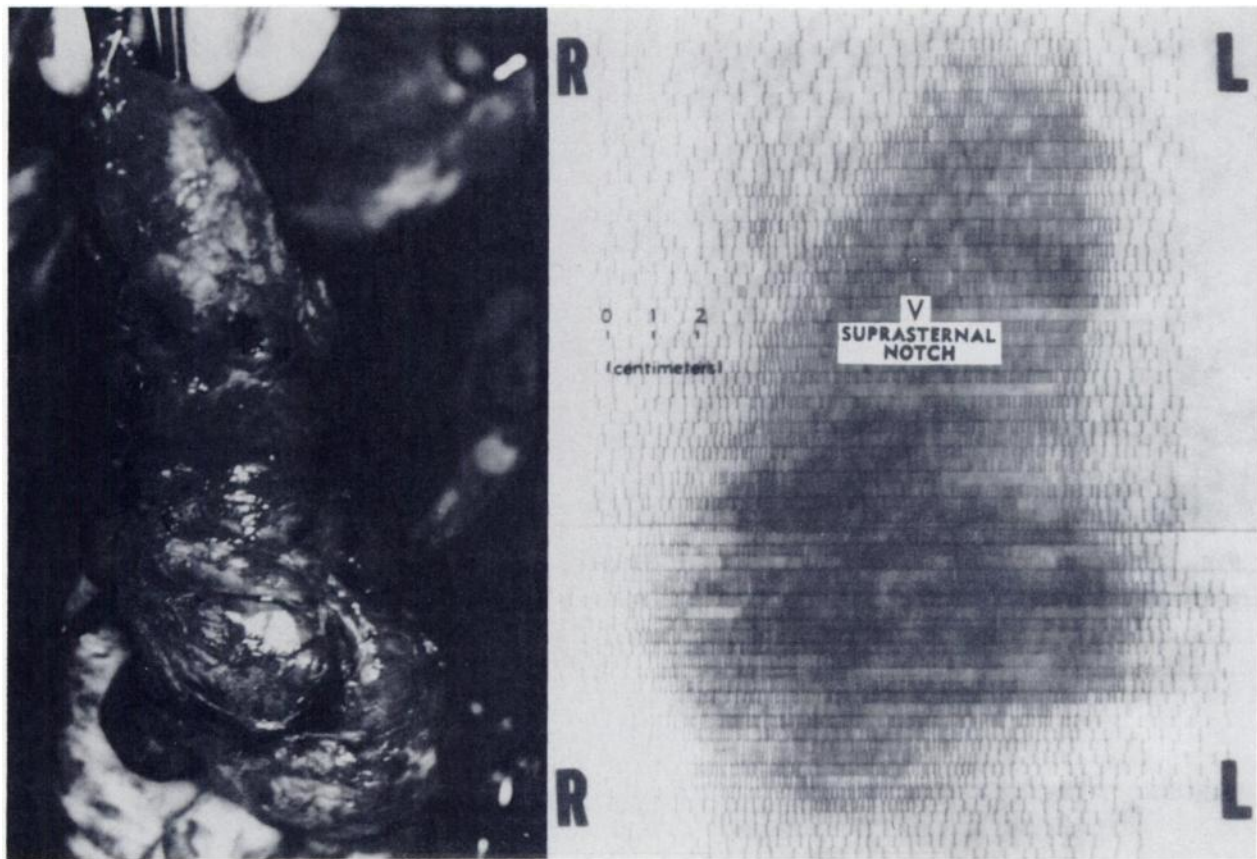
Serum T <sub>4</sub> and T <sub>3</sub>	No. patients
Elevated T <sub>4</sub> and T <sub>3</sub>	8
Elevated T <sub>3</sub> only	2
Elevated T <sub>4</sub> only	7
Total	17

surgically treated patients had a massive substernal goiter. Surgery was successful and uncomplicated, but sternal splitting was needed. Figure 2 shows the gross surgical specimen and the preoperative thyroid image. The other patient had a massive cervical goiter, atrial fibrillation, and congestive heart failure. After a brief treatment of the cardiac problem, surgery was done without untoward incident. The antithyroid drug-treated patient had a massive goiter with good control of hyperthyroidism on propylthiouracil for 10 yr. He refused the option of radioiodine or surgery.

A breakdown of the initial radioiodine therapy doses is given in Table 5. Fifteen of 32 patients received initial doses of 50 mCi or larger. In spite of the large doses employed, only 25 (78%) of the patients were successfully treated with a single dose of radioiodine. Five patients were successfully treated with a second dose. Repeat radioiodine doses were 25 to 30 mCi for four of these patients, and the remaining patient received a second dose of 100 mCi. Two patients, one of whom received 75 mCi, and the other 50 mCi, were not successfully treated with the initial dose, refused a second therapy dose of iodine-131, and died of complications of hyperthyroidism within a few months. Clinical radiation thyroiditis and exacerbations of hyperthyroidism were not observed in any of these patients.

Twenty-two of the 30 successfully treated patients were euthyroid after radioiodine therapy without replacement thyroid hormone. Three of these patients received two doses of radioiodine. Correlating with the low rate of hypothyroidism in TMNG patients is the observation that persistent goiter was the rule, being present in 25 of 28 patients for whom data was available.

Duration of followup for TMNG patients was relatively short, ranging from a few months to 14 yr (average 4.65 yr). This short duration of followup relates primarily to the short life expectancy of these elderly patients. Ten of the 35 patients with large TMNG are known to have died from causes unrelated to their thyroid conditions, ten others cannot be traced, and seven were 77 yr or older when last seen. As already noted, two patients died within a few months of an unsuccessful initial dose of radioiodine. The remaining patients survived 1 or more years with no further thyroid problems.



**FIGURE 2**  
Surgical specimen and image for massive substernal TMNG that required sternal splitting to excise. Surgeon's finger tips, holding up specimen, gives indication of size of goiter

## DISCUSSION

The clinical and laboratory features that have traditionally been described as distinguishing TMNG from Graves' disease were present in our patients. Perhaps less well known is the frequency of  $T_4$  toxicosis, 41% in this series. It is important to distinguish  $T_4$  toxicosis from various types of euthyroid hyperthyroxinemia (7,8). Of primary value in this differentiation is the clinical evaluation. A history of unexplained weight loss with increased appetite, tachycardia, atrial fibrillation (with or without heart failure), tremor of recent onset, heat intolerance, and the presence of a large multinodu-

lar goiter are most helpful. TRH testing may also be of value. A normal response would exclude hyperthyroidism. The blunted responses obtained in these patients were consistent with, but were not unequivocal evidence of hyperthyroidism. Blunted TRH tests may be seen in euthyroid elderly sick patients, particularly if malnourished. Actually, any of the above findings may be found in euthyroid patients, but the more complete the spectrum, the more certain the diagnosis of  $T_4$  toxicosis. Our experience with these and other hyperthyroid patients (especially elderly) provides support for the contention that  $T_4$  toxicosis may be more common than has heretofore been appreciated (9).

"Why Not Radioiodine Therapy for Toxic Nodular Goiter?", an article published in 1967 (10), cited 16 references advising against that treatment. However, it was observed that good results were achieved even by those who argued against radioiodine. Principal arguments against the treatment included: (a) possibility of associated malignancy; (b) surgical treatment is quicker; (c) radioiodine does not eliminate the goiter; and (d) radioiodine does not relieve hyperthyroidism with certainty in TMNG. None of the arguments were persuasive at that time, and no subsequent data has been presented that would alter that conclusion. Carcinoma

**TABLE 5**  
Initial Radiolodine Doses for Patients with Large TMNG

Radiolodine dose mCi	No. patients
25-30	17
50	2
75	4
90-100	6
150	1
200	2
Total	32

in TMNG is so uncommon that it is difficult to find even a case report. I have not seen one case in my 25-year experience. Surgery may be quicker, but if the time required to prepare the patient is considered, there is little difference if the initial dose of radioiodine is effective. The risks of surgery in these older people, many of whom have heart disease, is obvious. The survival of our elderly patient with heart disease shows that the surgical option may be viable if an experienced thyroid surgeon is available. It is true that the goiter is seldom eliminated by radioiodine therapy. This is the natural consequence of the large amount of degenerated tissue that does not concentrate the radioiodine. Nevertheless, obstructive complaints after radioiodine therapy are exceedingly uncommon. Because all of our radioiodine-treated patients responded to one or two doses of therapy (excepting two who refused further treatment after initial unsuccessful doses, and died of complications of hyperthyroidism), the argument that radioiodine is unreliable seems untenable, providing the therapist is generous with his dosage.

If one plans radioiodine therapy for patients with large TMNG, more specific dosimetry instructions are needed beyond the concept that higher doses are required than those for Graves' disease. As previously noted, it is impossible to make any reliable estimate of the weight of functioning parenchyma in a large TMNG. Hence, dosimetry is essentially empirical. Our plan of delivering 200  $\mu$ Ci per gram of estimated weight, about twice the dose commonly employed for Graves' disease, has been effective. In this formulation a 100 g goiter with a 25% RAIU would receive 80 mCi. The 80 mCi dose seems high in absolute terms, but it is a simple consequence of the two basic factors in dosimetry. The RAIU is relatively low, and the goiter tends to be quite large. From this point of view, it is easier to understand why a 250 g goiter with a 25% uptake might be treated with 200 mCi. Even the 100  $\mu$ Ci per gram dose commonly used for Graves' disease would call for a 100 mCi dose in such a patient.

Reluctance to use single doses this high had led to fractional treatment in which the eventual total dose was no less, but the duration of the illness was considerably prolonged. In addition, there is always the risk that an initial ineffective dose of radioiodine may reduce the

subsequent RAIU so that even higher doses might be required eventually to complete the treatment. This risk was relatively small, for only one of the five patients who received more than one dose of radioiodine had a RAIU value less than 20% prior to the second dose.

The safety of radioiodine therapy, especially the large doses herein advocated, may be questioned. In elderly fragile patients there is the possibility of an exacerbation of the hyperthyroidism by radiation induced discharge of preformed thyroid hormone. Cerebral emboli following radioiodine therapy had been reported in similar patients (11). Pretreatment with large doses of antithyroid drugs should be liberally employed in these patients (12) as protection against these potential hazards. No complications of these types were experienced in our patients.

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