

# Treatment of Thyrotoxicosis\*

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In this review, the causes of thyrotoxicosis and the treatment of syndromes with increased trapping of iodine are discussed. The benefits and the potential side effects of 3 frequently used therapies—antithyroid medications, thyroidectomy, and  $^{131}\text{I}$  treatment—are presented. The different approaches to application of  $^{131}\text{I}$  treatment are described. Treatment with  $^{131}\text{I}$  has been found to be cost-effective, safe, and reliable.

**Key Words:** thyrotoxicosis; antithyroid medications;  $^{131}\text{I}$  treatment; thyroidectomy; Graves' disease; toxic nodular goiter

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**T**hyrotoxicosis occurs in 2% of women and about 10% as often in men (1–3). Any or all systems of the body can be affected, but the symptoms and signs can be variable in individual patients (Table 1). A simple way of classifying the various causal disorders is to measure free thyroxine ( $\text{T}_4$ ) and thyrotropin (thyroid-stimulating hormone [TSH]) and to determine 24-h uptake with  $^{123}\text{I}$  (Table 2). Diseases with increased uptake, including Graves' disease and single or multiple functioning nodules, generally require long-term management. Graves' disease is the most common cause of thyrotoxicosis and is attributable to immunoglobulins that activate the TSH receptor of follicular cells. In some cases of hyperfunctioning nodules, the cause is a mutation in the TSH receptor that results in the receptor functioning in the absence of TSH (4). In these disorders, there is truly a hyperthyroid gland. In contrast, many thyrotoxic diseases are characterized by a low uptake of iodine, and the gland is not hyperthyroid. Most of these conditions are transient and do not require long-term therapy. Included in this category are the ingestion of excess thyroid hormone (transient provided that the dose can be reduced) and thyroiditis. This review focuses on the former group of conditions, specifically, Graves' hyperthyroidism and hyperfunctioning nodule diseases.

There are 3 distinct treatments for these conditions, antithyroid medications, thyroidectomy, and radioiodine ( $^{131}\text{I}$ ).

Different specialists in the United States and specialists in various countries might recommend different treatments for patients with identical conditions (5,6). Each of the treatments is described here, but there is an emphasis on  $^{131}\text{I}$ . One long-term Swedish study compared patients' impressions of physical and mental wellness many years after medical, surgical, or  $^{131}\text{I}$  therapy. There was little difference among the treatments. All groups had more fatigue than people from the general population (7). However, 49% of these patients still had abnormal thyroid function, the majority with low or suppressed TSH, stressing the point that these conditions are life-long illnesses that need periodic biochemical monitoring, even after apparently successful treatment. Another study indicated that patients do not receive adequate information about treatment options; therefore, a priority for physicians should be to provide enough time to discuss treatment options and to address each patient's questions and concerns (8).

The treatment of pediatric thyrotoxic patients and pregnant thyrotoxic patients is included in this review. The relationship between the orbitopathy of Graves' disease and the treatment of hyperthyroidism is discussed.

## DIAGNOSTIC TESTING

It is very important to establish that a patient is thyrotoxic by demonstrating a low level of serum TSH and an elevated level of free  $\text{T}_4$  or free triiodothyronine ( $\text{T}_3$ ) (or both). There is a trend toward measuring only TSH, but knowledge of the free hormone levels provides information about the severity of the disorder, which can be masked clinically in some patients, particularly older patients (9,10). Once the thyrotoxic state is established, measurement of the uptake of a  $^{123}\text{I}$  tracer is recommended to allow the stratification of patients (11–13). We schedule measurement of the 24-h uptake of  $^{123}\text{I}$  on the day of treatment with  $^{131}\text{I}$ . A specific therapeutic dose can be delivered as a capsule or liquid within 2 h of the diagnostic testing. This procedure streamlines testing and treatment but may not be possible for all physicians responsible for administering  $^{131}\text{I}$ . There has been no controlled trial to determine the reproducibility of uptake measurements with specific delays. We believe that a measurement obtained more than 1 mo before therapy should be repeated to ensure that no significant change has occurred. An uptake measurement is

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**TABLE 1**  
Symptoms and Signs of Thyrotoxicosis

Symptoms	Signs
Weight loss	Tachycardia
Nervousness	Sweatiness
Palpitations	Feeling hot
Feeling hot or sweatiness	Fine tremor
Loose bowel movements	Atrial fibrillation
Poor stamina	Restlessness
Breathlessness	Apathy (older people)
Tremulousness	Weight loss
Poor concentration	Goiter*
Changes	Eye signs*
	Pretibial* dermopathy
	Finger clubbing*

\*Features specific to Graves' disease.

strongly recommended to ensure that patients with low uptake, such as those with silent thyroiditis, are not treated with <sup>131</sup>I.

### TREATMENT OF GRAVES' DISEASE

The logical treatment for Graves' disease would be to remove the cause, which is the thyroid-stimulating immunoglobulin (TSI) (14,15). Immunosuppressive therapy is not successful and is potentially dangerous (16).

### ANTITHYROID MEDICATIONS

Several reviews have covered the topic of antithyroid medications (15,17–20). Antithyroid medications have been available for more than 60 y; those in current use are methimazole (carbimazole in the U.K. and countries influenced by British medicine) and propylthiouracil. The longer half-life of methimazole allows for once-daily intake, which is a considerable advantage over the dosage schedule for propylthiouracil, which generally has to be

**TABLE 2**  
Causes of Thyrotoxicosis

High uptake of iodine	Low uptake of iodine
Graves' disease (Basedow's disease)	Exogenous thyroid hormone
Functioning nodule	Medicamentous
Toxic multinodular goiter	Factitious
Pituitary tumor secreting excess TSH	Dietary (hamburger thyrotoxicosis)
Tumors of placenta secreting large quantities of human chorionic gonadotropin	Thyroiditis
	Subacute
	Silent
	Postpartum
	Excess iodine
	Jodbasedow
	Amiodarone
	Uptake at other sites, struma ovarii, functioning thyroid metastases

taken 2 or 3 times daily (19). For reasons discussed later in this review, propylthiouracil is preferred during pregnancy. The main action of these drugs is to interfere with the iodination of tyrosine within the colloid of the thyroid follicle. The drugs have a minor immunologic effect that is not entirely attributable to the normalization of thyroid function. The inhibition of the conversion of T<sub>4</sub> to T<sub>3</sub> by propylthiouracil is of minor significance. Both medications are introduced in a loading dose for about 4–6 wk. As the patient's condition improves symptomatically and biochemically, the dose can usually be reduced. Daily loading doses of 10–30 mg of methimazole or 100–300 mg of propylthiouracil are appropriate for most patients, and the lower end of the range is advised for mild disease. There is growing evidence that 10 mg of methimazole is effective for the majority of patients. Maintenance doses of 5–10 mg of methimazole or 50–100 mg of propylthiouracil twice daily keep most patients euthyroid. For patients who cannot take medications by mouth, propylthiouracil has been administered rectally (21). When neither of these routes can be used, intravenous methimazole has been administered (22).

Medication is prescribed for 12–18 mo with the hope that the disease will remit. Remission can be expected in 20%–30% of patients in the United States and somewhat higher percentages in Europe and Japan. Although there is no clinical sign or laboratory test that uniformly predicts patients whose disease will remit, mild disease of short duration, a small thyroid, the absence of a family history of Graves' disease, and normalization of TSI are somewhat helpful. When the disease relapses after the cessation of antithyroid medication, a decision can be made to conduct another course of antithyroid drug or to proceed to radioiodine therapy.

An alternative medical approach is to continue the larger loading dose for 18 mo and to add thyroid hormone (block-and-replace therapy). This approach was thought to increase the percentage of patients whose disease would remit, but a meta-analysis failed to confirm this notion (17).

Patients should be educated about the side effects of the medications, and some authorities provide the information both orally and in writing. Mild complications include maculopapular and urticarial skin rashes, nausea, dislike of the taste of the medications, and arthropathy. We advise discontinuing the offending drug and, after the adverse symptoms or signs have resolved, trying an alternative medication. There is some crossover of side effects, and patients and physicians should be alert to the reappearance of the complications with the alternative medication. More serious is agranulocytosis, which occurs most often within weeks of starting either medication and usually presents as a sore throat with fever. Patients must be warned to stop the drug and have an immediate differential white cell count test. When the granulocyte count is less than 1,500/mm<sup>3</sup>, the medication should not be restarted and an alternative medication should not be prescribed. This serious complication occurs in approximately 0.35% of patients but is rarer when

the dose of methimazole is lower than 30 mg daily. Methimazole can also cause an obstructive liver disorder; rarely, propylthiouracil causes hepatic necrosis and liver failure that can require transplantation. Most authorities accept that it is not possible with periodic laboratory testing to identify these serious complications at the earliest phase; therefore, vigilance by the physician and repeated education of the patient are important.

Antithyroid medication has a significant role in rendering patients euthyroid before treatment with  $^{131}\text{I}$  or thyroidectomy (23–25). For radioiodine, this process is advised for older patients (arbitrarily designated as 50–60 y old), very thyrotoxic patients, and patients with cardiac problems. All patients being treated by surgery should be euthyroid first. There is some evidence that propylthiouracil increases the resistance of the thyroid to radiation (26,27). In contrast, methimazole and carbimazole do not, and the outcome achieved after  $^{131}\text{I}$  treatment is equal to or better than that achieved when no medication is administered (28–30). Propylthiouracil is discontinued for 3 d and methimazole is discontinued for 5 d before testing and therapy.

## SURGERY

Some surgeons promote thyroidectomy as the treatment of choice for Graves' disease (31). However, at present very few patients with uncomplicated Graves' disease are treated by surgery, as confirmed by Wartofsky et al. in a study quantifying the advice of experts on thyroid disease in the United States, Europe, and Japan (6). Indications for surgery include a coexisting nonfunctioning nodule or a nodule suggestive of cancer on fine-needle aspiration. One example of the latter is a patient who desires to become pregnant and who is not convinced that it is safe to be treated with  $^{131}\text{I}$  before conception or to take antithyroid medication during pregnancy. In 1 clinic where patients had access to an endocrinologist, a nuclear medicine physician, and a surgeon, 15% elected thyroidectomy (32). In the first 100 patients treated by surgery, 4 incidental thyroid cancers were found. This proportion is significantly greater than that seen after  $^{131}\text{I}$  treatment and supports the concept that millimeter-sized cancers are ablated by radiation. In practice, access to 3 specialists would not be easy, and it is hoped that 1 physician would present the advantages and disadvantages of each approach and then provide unbiased advice about the best treatment for each patient.

Lal et al. reported on 103 surgical patients (mean  $\pm$  SD age,  $34.3 \pm 13.9$  y) for whom the indications were patient preference (26%), cold nodule (24%), eye symptoms (20%), large goiter size (18%), allergy to antithyroid medications (15%), and young age (14%) (31). In another series, eye involvement was also used as an indication for thyroidectomy, and there was improvement in 130 of 500 patients (33). Thyroidectomy is indicated occasionally in a patient with amiodarone-induced thyrotoxicosis that fails to respond to medical therapy.

The procedure should be a nearly total thyroidectomy with the expectation for lifelong thyroid hormone replacement. The incidence of recurrence after subtotal thyroidectomy is high, and this almost always should be treated with  $^{131}\text{I}$ . Thus, the patient receives radioiodine treatment which, for one reason or another, was originally believed to be less desirable. A surgeon who is experienced in thyroidectomies and who performs many each year should be sought, and complications, such as hypoparathyroidism and damage to the recurrent and superior laryngeal nerves, should be uncommon. Toxic goiters with single or multiple nodules can be treated by surgery or  $^{131}\text{I}$  treatment as discussed later in this article (34). Surgery provides a more rapid outcome and should be considered in a patient who wishes an early conception or is concerned about radiation (35).

## HISTORICAL BACKGROUND FOR $^{131}\text{I}$ TREATMENT

The first reports on the use of  $^{131}\text{I}$  to treat hyperthyroidism (36) appeared in 1942 (37,38). Over more than 6 decades,  $^{131}\text{I}$  treatment has proven to be an effective, cost-effective, and safe therapy for thyrotoxicosis. Although its use has spread worldwide, controversies still exist, including the selection of patients, the goal of therapy, and how best to calculate the therapeutic dose.

## GOAL OF TREATMENT

There has never been any debate that the goal of  $^{131}\text{I}$  treatment is to cure the thyrotoxic condition. However, there used to be considerable debate about whether the goal of  $^{131}\text{I}$  treatment was to render the patient euthyroid without the need for thyroid hormone or to reduce the function to below normal and replace L-thyroxine. It is now generally accepted that titrating the administered dose to render all patients euthyroid is not possible or wise. Historically, some patients treated with very small doses remained euthyroid without needing replacement therapy, and a few became hypothyroid. However, these data should not be used as an argument for treating all patients with small doses, because the majority of patients treated that way remain hyperthyroid and need to be retreated. For example, in 1 report, at 4.5 y after treatment, only 45% of patients were euthyroid after 1 dose and 80% were euthyroid after 2 or more doses (39). The same group of investigators administered 74 MBq (2 mCi) every 6 mo; 38% of patients were euthyroid after a single dose, confirming that there would be a significant delay in achieving cure of thyrotoxicosis (40). Some patients treated only with antithyroid medications and no  $^{131}\text{I}$  become hypothyroid on long-term follow-up. Therefore, it is impossible to believe that all patients will be euthyroid without L-thyroxine replacement after  $^{131}\text{I}$  treatment. The dose of  $^{131}\text{I}$  should be sufficient to cure hyperthyroidism in a reasonable time (<6 mo), and both patients and physicians should recognize and accept that thyroid hormone replacement will be required.

## HOW IS ADMINISTERED DOSE DETERMINED?

There are 2 common approaches for determining the administered dose (41). One is to prescribe a fixed dose for all patients. The other is to calculate a dose based on the size of the thyroid and its percentage uptake at 24 h. Fixed doses vary but are commonly in the range of 185–555 MBq (5–15 mCi). A variation on the fixed-dose theme is to add an incremental dose of  $^{131}\text{I}$  when the gland is large or when the uptake is relatively low. That concept, now similar to the calculated method, will be discussed below.

Watson et al. reported success rates of 72.4% for Graves' disease patients treated with 185 MBq (5 mCi) of  $^{131}\text{I}$  (42). Over a median follow-up period of 5.5 y, retreatment was required for 25.6%, with 3.5% requiring more than 2 doses. At the 5-y follow-up, 27.3% were hypothyroid. Another study reported that 74.5% of patients were euthyroid or hypothyroid at 12 mo after a single dose of 185 MBq (5 mCi) (4). Very low doses of  $^{131}\text{I}$  (mean, 103.6 MBq) resulted in a high incidence of persistent disease (39%) but did not necessarily result in a low incidence of hypothyroidism (25%). A dose of 370 MBq (10 mCi) of  $^{131}\text{I}$  for toxic diffuse goiter resulted in 50% hypothyroidism within 3 mo and 69% hypothyroidism by 1 y of treatment (43). Using a fixed dose of 555 MBq (15 mCi) of  $^{131}\text{I}$ , Ratcliffe et al. reported hypothyroidism in 48% of patients and euthyroidism in 32%, but additional  $^{131}\text{I}$  therapy was required in 19% (44). In an analysis of 227 patients treated with 555 MBq (15 mCi), 64% of patients were hypothyroid and only 5.6% had failed to become euthyroid within 1 y (45). These data confirm that larger fixed doses are more reliable in controlling hyperthyroidism. They also serve as a reminder that hypothyroidism is to be expected and that a follow-up protocol should be arranged.

## CALCULATING ADMINISTERED DOSE

Alexander and Larsen used the formula  $(296 \text{ MBq [8 mCi]} \times 100)/(\text{percentage uptake at 24 h})$  for calculating the administered dose, thus excluding the size of the thyroid from the calculation. In their study, 86% of patients were euthyroid or hypothyroid at 1 y after treatment. The mean  $^{131}\text{I}$  dose was 540 MBq (14.6 mCi) (46).

However, many use a formula that is based on gland size and uptake for calculating the administered dose:  $(Z \times \text{size of thyroid [g]} \times 100)/(\text{percentage uptake at 24 h})$ ; in this formula, Z is the desired number of becquerels or microcuries administered per gram. Z ranges from 3.7 to 7.4 MBq (100–200  $\mu\text{Ci}$ ), in our experience, 5.9 MBq (160  $\mu\text{Ci}$ ). That value (160 mCi) was accepted after trials by 1 of the authors and other investigators demonstrating an unacceptable incidence of treatment failure with lower doses (47,48). Therefore, a 40-g gland with 50% uptake would be treated with 474 MBq (12.8 mCi). This method has a high probability of cure with a single dose of  $^{131}\text{I}$  and less than 10% of patients needing to be retreated.

The administration of a quantity of  $^{131}\text{I}$  on the basis of the size of the thyroid implies that the exact size is known. This size can be determined with some accuracy by ultrasound. Experience can be developed by estimating the weights of thyroid glands before ultrasound. Likewise, estimation of the weights of glands to be removed surgically can be compared with the true weights. Finally, an empiric system using 1, 2, and 3 times normal thyroid volume can be used. Twenty grams is the normal reference size used most often. There is a tendency to underestimate the sizes of very large glands. In the past, the area of the thyroid could be determined from rectilinear scanning and transformed into a volume, but few clinics have this instrumentation. Pinhole images are not recommended for the determination of size.

## CALCULATING ABSORBED DOSE

Controversies exist with regard to the radiation dose to the thyroid needed to successfully treat Graves' disease. A study comparing doses of 150, 300, and greater than 300 Gy to the thyroid found no significant difference in the rates of recurrent hyperthyroidism (150 Gy: 15%; 300 Gy: 14%; and  $\geq 300$  Gy: 14%;  $\chi^2$  test,  $P = 0.72$ ), whereas the rates of hypothyroidism in the 3 groups were significantly correlated with doses (150 Gy: 30%; 300 Gy: 46%; and  $\geq 300$  Gy: 71%;  $\chi^2$  test,  $P = 0.0003$ ) (49). Howarth et al. compared low radiation doses to the thyroid (60 vs. 90 Gy), trying to minimize the number of patients requiring thyroid hormone replacement after  $^{131}\text{I}$  therapy (50). Euthyroidism was achieved in 46% of the patients, and 47% were rendered hypothyroid at the final follow-up (median, 37.5 mo). A dose of 60 Gy yielded a 39% response rate at 6 mo while minimizing early hypothyroidism, but no significant advantage in the response rate was gained with a dose of 90 Gy. For a more rapid therapeutic effect, the authors recommended doses in excess of 120 Gy, recognizing that there will be an increased rate of hypothyroidism. Other reports in which 80 Gy of  $^{131}\text{I}$  was used showed that 23.1% of the patients were still hyperthyroid at 1 y after treatment, 69.2% were euthyroid, and 7.7% were hypothyroid (51). Lower doses to the thyroid, such as 50 Gy, resulted in 33% of the patients having persistent hyperthyroidism (52). Bajnok et al. used a fixed dose of 70 Gy of  $^{131}\text{I}$  but increased it up to 100 Gy for large glands (53). They also suggested that no increase in the target dose over 100 Gy is needed.

Traino et al. evaluated what activity to administer on the basis of the desired volume reduction in the thyroid gland and compared the results with those of a fixed-dose regimen (54). The authors argued that a method based on volume reduction may reduce the thyroid absorbed dose and thus allow  $^{131}\text{I}$  therapy to be optimized. The same group published a predictive mathematic model for the calculation of the final mass of a thyroid gland affected by Graves' disease and treated with  $^{131}\text{I}$  (55). Haase et al. concluded that the thyroid volume after treatment correlated significantly

with the clinical outcome of the treatment and suggested that an adjustment of the target dose based on the thyroid volume before treatment may affect the outcome (56).

### SELECTION OF DOSE OF $^{131}\text{I}$ IN PRACTICE

For thyroid glands of average size and uptake, fixed doses of  $^{131}\text{I}$  are effective, provided that sufficient  $^{131}\text{I}$  is administered. Each therapist needs to select the preferred dose but should analyze the outcome; 370–555 MBq is an appropriate range. Similarly, those who use a formula for calculating the administered dose should not have to retreat a significant proportion of patients when doses of 5.55–7.4 MBq (150–200  $\mu\text{Ci}$ ) are used. The same applies to those who calculate the specific absorbed dose.

### ALTERNATIVE RADIONUCLIDES OF IODINE

Several other radionuclides of iodine have been used to treat hyperthyroidism. Several authors reported on  $^{125}\text{I}$ . The theory was that the low-energy Auger electrons would not cause sufficient nuclear radiation to kill the cells and long-term euthyroidism might be achieved. In practice, this was not the case (57).

### FAILURE OF THERAPY

The need for retreatment indicates that insufficient  $^{131}\text{I}$  was administered. This situation could result because a fixed dose was too small relative to the size of the gland or because the thyroid was less able to trap iodine than expected (58). Alternatively, it could result because the size of the gland was underestimated when a dose per gram corrected for uptake was administered. A rapid turnover of iodine must be considered and can be adjusted for by measuring 24-h uptake rather than uptake at 4–6 h (59,60). Although it is very rare for early uptake to be elevated and 24-h uptake to be normal, early uptake can be higher (61,62). Therefore, those who always rely on early uptake will treat some patients with a lower dose of  $^{131}\text{I}$  and have a higher failure rate.

Recently, another rare cause of failure was described: a patient “spat up” the capsule and also had a high level of serum iodine (63). When a patient is not rendered euthyroid or hypothyroid, a second treatment is advised. Some authorities advise a second treatment after 3 mo; we prefer a delay of 6 mo or more because a proportion of patients respond later.

### TREATMENT OF SINGLE HYPERFUNCTIONING AUTONOMOUS NODULE

Autonomous hyperfunctioning nodules (64) are more common in regions of iodine deficiency. The diagnosis of single autonomous nodules as a cause of thyrotoxicosis is established by a suppressed TSH level and a  $^{123}\text{I}$  scintiscan demonstrating a functional nodule with suppression of the normal thyroid. A functioning nodule secretes proportionately more  $\text{T}_3$  and is a cause of  $\text{T}_3$  toxicosis best defined by

the measurement of free  $\text{T}_3$  and TSH. In virtually all patients, there is a very slow progression to the thyrotoxic state, and there is some evidence that the volume of functioning tissue must be sufficiently large to secrete excess hormone (65,66). A surrogate is the diameter of the nodule, and most nodules causing thyrotoxicosis are 3 cm or larger. Once the patient is thyrotoxic, there is almost no chance of remission, although in a few cases necrosis of the center of the nodule results in euthyroidism (67); however, that remission is not long-lasting. As a result, the decision to remove the nodule by lobectomy or to ablate it with  $^{131}\text{I}$  is generally accepted. Each treatment has benefits and drawbacks. Lobectomy is undertaken after the patient is rendered euthyroid by antithyroid medications. It produces a speedy cure, there is no radiation, but it requires surgery, usually under general anesthesia.  $^{131}\text{I}$  treatment avoids surgery and anesthesia but requires radiation safety education and planning.  $^{131}\text{I}$  takes several weeks to have its full effect, and the nodule will not dissolve completely; therefore, the patient must be advised that physicians may want to perform follow-up examinations. Some authorities advise surgery over  $^{131}\text{I}$  treatment on the basis of costs and outcomes, including risks of treatments (34,64).

The administered dose of  $^{131}\text{I}$  can be empiric or calculated from the volume of the nodule and its fractional uptake of iodine. Empiric fixed doses of  $^{131}\text{I}$  are frequently determined by the quantity that would not require hospitalization of the patient on the basis of local and national regulations. The arguments for and against this philosophy are that it is simple and effective for most patients. However, it means that patients with nodules of different volumes and different levels of uptake are treated the same. The doses range from 370 MBq to 1.1 GBq (10–30 mCi) (68). Various reports have described contradictory findings. In 1 study, the failure rate after the administration of 370 MBq (10 mCi) was 10%, with a follow-up of up to 3 y (69). Nodules with diameters of less than 3 cm were cured, suggesting that larger doses are needed for larger lesions. Using a fixed dose of 740 MBq (20 mCi) of  $^{131}\text{I}$ , Huysmans et al. reported a failure rate of only 2%, with a follow up of  $10 \pm 4$  y (70). The incidence of hypothyroidism was 6%. Another study advised fixed doses of 370 MBq (10 mCi) in younger patients and in patients with mild thyrotoxicosis, whereas doses of 555–740 MBq (15–20 mCi) should be considered for larger goiters (71).

Ceccarelli et al. administered 7.4 MBq (200  $\mu\text{Ci}$ ) of  $^{131}\text{I}$  per gram corrected for uptake (72). A single dose of  $513 \pm 158$  MBq ( $13.9 \pm 4.3$  mCi) had a success rate of 94%, and 60% of their patients were hypothyroid by 20 y (72). The volume can be determined by ultrasound ( $4/3 \times 22/7 \times r1 \times r2 \times r3$ ), and the uptake can be determined with a  $^{123}\text{I}$  tracer. The volume of a 4-cm nodule is 8 times that of a 2-cm lesion and would theoretically require 8 times the dose for an equivalent effect. This formula is the same as the formula that we use:  $(7.4 \text{ MBq } [200 \mu\text{Ci}] \times \text{mass of nodule} \times 100)/\text{uptake}$ . Patients seldom have to be retreated, but

hypothyroidism occurs with a higher frequency than was previously reported (73).

Another method for calculating the  $^{131}\text{I}$  dose is to determine the ratio of the dose to the nodule area. A dose to the nodule area of 37–55.5 MBq/cm<sup>2</sup> appears to be optimal and avoids hypothyroidism (74).

Huysmans et al. compared the outcomes of regimens involving fixed doses and calculated doses adjusted for thyroid weight and radioactive iodine uptake (75). At the end of the follow-up, hyperthyroidism was successfully reversed in 73% of the patients receiving fixed doses and in 88% of those receiving individualized doses. A total of 66% of the patients were adequately treated with a single calculated dose; in comparison, 27% were adequately treated with a single empiric dose. Thus, calculated doses appear to be preferable to fixed doses.

Finally, the administered dose can be calculated to deliver a specific dose defined in rads or grays to the nodule. A recent study of 425 treated patients demonstrated that doses of 300–400 Gy delivered to the nodule were successful in 90%–94% of patients (76).

By the time that a patient is thyrotoxic, the functioning nodule produces sufficient thyroid hormones that TSH is suppressed. As a result, the normal thyroid tissue is not seen on a scintiscan. In milder cases, there can be some trapping of iodine by normal cells, and they will be irradiated. Gorman and Robertson have calculated that the contralateral lobe can receive 2,300 rads (23 Gy) when the goal is to deliver 30,000 rads (300 Gy) to the functioning nodule (77). The contralateral lobe will receive a higher dose when it is not completely suppressed. In the past, liothyronine was administered to render the patient more thyrotoxic and to suppress TSH further in an effort to reduce the uptake in normal cells. This approach is potentially dangerous in older patients and is not recommended. Patients showing this scintigraphic pattern should be advised that hypothyroidism could be the outcome after  $^{131}\text{I}$  therapy. In reviewing the literature, we were interested to find this approach being used in cats with mild thyrotoxicosis attributable to functioning nodules (78).

Other therapeutic options for autonomous hyperfunctioning thyroid nodules include ultrasound-guided laser thermal ablation and percutaneous ethanol injection (79). Most of the published data on the percutaneous injection of alcohol are from outside the United States, in particular, Italy (80,81). Several injections of alcohol are administered to the nodule by use of ultrasound to localize the appropriate site. Free hormone levels fall, TSH levels rise, and the volume of the nodule decreases. The advantages include no surgery or exposure to radiation. The disadvantages are multiple visits (occasionally more than 10), pain and, in rare cases, serious local complications, such as necrosis of the larynx (82). Zingrillo et al. compared a  $^{131}\text{I}$  dose of 12.5 MBq/mL with  $^{131}\text{I}$  plus percutaneous ethanol injection. Both regimens achieved high rates of success at a 12-mo follow-up (91% and 100%, respectively) (83).

## TOXIC MULTINODULAR GOITERS

The distinction between an autonomous hyperfunctioning nodule and a toxic nodular goiter is blurred. A scintiscan of a solitary hyperfunctioning nodule frequently demonstrates other small regions of nonsuppressible function. In addition, pathologists usually can demonstrate other nodules at autopsy in addition to the dominant lesion. Once the patient is thyrotoxic, spontaneous remission is not to be anticipated, and the choice of therapy is surgery or  $^{131}\text{I}$  treatment. Because the affected patients are usually older, it is important to render them euthyroid with antithyroid medications before definitive therapy. In 1 study, 444 MBq (12 mCi) (range, 259–555 MBq [7–15 mCi]) were administered; 92% of 146 patients became euthyroid within 3 mo, and 97% became euthyroid at 1 y. Four (3%) became clinically or biochemically hypothyroid (84). A similar study of 130 patients also found that 92% were cured, but a high proportion needed a second treatment (85). The investigators administered 3.7 MBq (100  $\mu\text{Ci}$ ) per gram corrected for uptake and measured the volume of the gland by ultrasound. Our approach is to deliver 7.4 MBq (200  $\mu\text{Ci}$ ), a dose calculated from the 24-h uptake and the volume determined by ultrasound. When the uptake is low, it can be increased with recombinant human TSH; we recognize that the latter is not approved by the U.S. Food and Drug Administration for this purpose (86–88).

## SIDE EFFECTS AND COMPLICATIONS

Acute radiation thyroiditis is very rare after  $^{131}\text{I}$  therapy of Graves' disease. It is painful and similar to subacute thyroiditis, with referral of the pain to the jaws and ears. Antiinflammatory medication or a short course of corticosteroids is of value. A thyroid storm can occur several days after therapy and is more common in older patients and those with severe disease—hence, the recommendation for the pretreatment of these patients with antithyroid drugs. There are rare reports of a thyroid crisis in children (89). There is an increase in mortality in the first year after treatment, mostly attributable to cardiovascular and cerebrovascular diseases (90,91). These data further support the argument for first rendering severely thyrotoxic patients and those at most risk euthyroid by medical therapy.

Long-term risks of theoretic concern include the potential for an increase in cancers, in particular, at sites in which radioiodine is concentrated, such as the thyroid, salivary glands, stomach, renal tract, bowel, and breasts. The large study of Ron et al. does not confirm this concern (92). There are also concerns that fertility will be reduced and that abnormalities in offspring will be increased. Several studies relate to the larger doses of  $^{131}\text{I}$  that are used to treat thyroid cancer. The consensus is that conception should be deferred for 12 mo and that maternal thyroid function should be normal (93,94).

## LITHIUM AS ADJUVANT TO $^{131}\text{I}$

Lithium reduces the release of thyroid hormones from the thyroid and has been used alone to treat hyperthyroidism.

Lithium has also been used as an adjuvant to  $^{131}\text{I}$  by retaining the radionuclide within the gland and delivering more radiation with a smaller administered dose. The results are conflicting, with some investigators finding more prompt control and higher reliability (95). In contrast, a large controlled study showed no difference between the effectiveness of the first therapy dose (68.4% for control group and 68.9% for lithium-treated group) and the overall cure rate (96.3% and 96.7%). Lithium has side effects, and we do not recommend its widespread use.

## RADIATION SAFETY

When a patient is treated with  $^{131}\text{I}$  and released, it is important that members of the public, including the family, are not exposed to significant radiation. The regulations vary between countries, but in the United States, there are 3 conditions under which outpatient therapy can be arranged. First, no adult can be exposed to 5 mSv (500 mrem). Second, patients can be released when the administered dose is  $\leq 1.22$  GBq (33 mCi). Third, the emitted radiation is  $\leq 7$  mrem/h at 1 m. For Graves' disease, these conditions are seldom a factor, but for large nodular thyroid glands, the calculated administered dose and hence the exposure of the public could be above these limits. Therefore, arrangements need to be documented that no one can receive more than 5 mSv (500 mrem) when patients are treated with doses that do not conform to the second and third requirements. Several studies have measured radiation rates to family members and have confirmed that simple measures, such as sleeping in a separate bedroom and remaining more than 2 m from family members for a few days, ensure that the regulations are fulfilled (96). In 1 investigation, the maximum exposure to a family member from the treatment of Graves' disease was 2.4 mSv (240 mrem); when detailed instructions were given, this exposure was reduced to 1.9 mSv (190 mrem) (97). As an example, a patient treated with 473.6 MBq (12.8 mCi) will emit 2–2.5 mrem/h at 1 m immediately after treatment and 1–1.25 mrem/h at 1 m after 24 h (50% uptake). There would need to be prolonged close contact for a member of the public to receive 5 mSv (500 mrem).

As an aside, cats can have hyperthyroidism, and radioiodine is an effective therapy (98). Radiation safety issues are more complicated for cats than for humans.

## AIRPORT SECURITY AND $^{131}\text{I}$ TREATMENT

There has been concern about terrorists bringing radioactivity into the United States with the intention of producing dirty bombs. Airports are armed with radiation detectors. To date, the alarms have captured only patients who have undergone testing or treatment with radionuclides or radiopharmaceuticals (99). A recent case report and editorial in the *British Medical Journal* illustrate this situation by describing the arrest and maltreatment of a patient who had Graves' disease and who had been treated

6 wk earlier (100). The absurdity of the alarm system is the attempt to identify levels of radiation double the background, levels that would be of no concern to public health. Patients should be advised of this risk; our policy is to give them a document describing the therapy and a measurement of emitted radiation made shortly before the intended flight.

## SPECIAL SITUATIONS

### Children

Most thyrotoxic children have Graves' disease (101). Children are less likely to have infiltrative orbitopathy, but there have been reports of eye disease, even in infants (102,103). There are geographic differences in how pediatric patients are treated (7). The incidence of side effects from antithyroid medications is higher in children, and they can be serious (104–106). Children are less consistent in taking the medications, and the remission rates are lower. When high doses of antithyroid medications are required for a long time, remission is unlikely (107). Thyroidectomy is technically more difficult in young children, and few surgeons are trained in this procedure. As a result, there has been increasing experience in the role and value of  $^{131}\text{I}$  treatment in pediatric patients (108,109). Major concerns are that  $^{131}\text{I}$  treatment might increase the risk of cancer and leukemia and have an adverse effect on fertility and offspring. Many studies have failed to confirm these concerns (110–112). Several authorities have promoted the administration of  $^{131}\text{I}$  earlier in the management of pediatric patients and even as the primary treatment. Children as young as 3 y can be treated (113). The administered dose can be determined as described earlier in this article. Some children have relatively large goiters, and the size can be calculated from length, width, and depth measurements obtained by ultrasound. This calculation provides a more exact size for treatment based on a dose per gram corrected for percentage uptake.

### Pregnancy

Graves' disease occurs in young women, and a patient may become pregnant before, coincidentally with, or after the diagnosis (114,115). The maternal thyroid dysfunction, the presence of TSI, and the management of the condition can all affect the fetus. Usually, the treatment consists of antithyroid medications, but maternal allergy to the medications presents a difficult management problem (116). Methimazole administered to the mother has been reported to cause aplasia cutis (a scarlike lesion of the scalp) and recently was linked to choanal atresia in offspring (117,118). Therefore, propylthiouracil is preferred. One group recommends monitoring the fetal size (119). It is very important to ensure that the mother does not receive diagnostic or therapeutic radioiodine when pregnant. There should be a mechanism to ensure that all women about to be tested with radionuclides of iodine are asked about the possibility of pregnancy and that all women who are to be treated have a negative pregnancy test. After 11 wk, the fetal thyroid

concentrates iodine, and if the fetus is exposed, it will be born athyrotic (120). Exposure of the fetus also reduces the intelligence quotient by 30 points per gray (100 rads) and introduces a slightly increased cancer risk (121). When exposure occurs in the first trimester, the risk of neonatal hypothyroidism is reduced considerably; an analysis by Stoffer and Hamburger demonstrated that it is safe to let the pregnancy continue (122). However, every effort should be made to ensure that such exposure does not occur. There is a legal precedent that a woman's verbal denial of pregnancy does not stand up as sufficient evidence in court to excuse the plaintiff (123).

### Thyroid Eye Disease

The management of thyroid eye disease is beyond the scope of this article (124). Eye disease is seen only in patients with autoimmune thyroid disease, such as Graves' disease and euthyroid Graves' disease. We shall focus on the relationship between eye disease and the method of treating Graves' hyperthyroidism and whether prophylactic measures are necessary (102,125,126). Data both for and against  $^{131}\text{I}$  causing or aggravating orbitopathy have been collected. It is clear that patients can have eye disease before being exposed to any specific treatment, and the original description by Graves confirms this notion. Historically, antithyroid medications were judged to be more likely to cause thyroid eye disease (127). One large study showed no difference in the onset of orbitopathy after antithyroid medications, thyroidectomy, or  $^{131}\text{I}$  treatment; similarly, there was no difference in the percentage of patients who had orbitopathy and whose disease worsened after the treatment of thyrotoxicosis (128). In contrast, Tallstedt et al. showed that  $^{131}\text{I}$  treatment caused a higher percentage of eye problems than medical or surgical treatment (129). In a follow-up study, the same investigators did not report this finding when L-thyroxine was introduced early after  $^{131}\text{I}$  treatment. Bartalena et al. showed that eye disease was more likely to occur with  $^{131}\text{I}$  treatment than with medical treatment (130). This finding was reversed when prednisone was prescribed for 3 mo to patients treated with  $^{131}\text{I}$ . Nevertheless, it is difficult to support the advice of those investigators (130) that all patients who have Graves' disease and are treated with  $^{131}\text{I}$  also receive prednisone, because only 5% developed a progressive eye problem. There is a growing body of evidence that smoking is a risk factor, and every effort should be made to encourage patients to stop this habit (131,132).

What can be learned from these data? Orbitopathy is part of Graves' disease. It can occur before, coincidentally with, or after the treatment of hyperthyroidism (133,134). When a specific treatment antedates the eye disease, it is likely that treatment will be incriminated. However, the timing could be coincidental. Discussion of the facts with the patient is important. Evaluation of the eyes before treatment and during follow-up is advised. When ophthalmic symptoms and signs are present or develop, referral of the

patient to an ophthalmologist and a thyroidologist knowledgeable in the management of orbitopathy is recommended.

### Chronic Renal Failure and Dialysis Patients

Administered iodine that is not trapped in the thyroid gland is cleared from the body largely by renal excretion. Thus, the selection of a dose for  $^{131}\text{I}$  therapy can be a challenging decision in patients with impaired renal function. Holst et al. reviewed the medical literature and concluded that the  $^{131}\text{I}$  dose does not need to be adjusted in patients who have end-stage renal disease and who are referred for the therapy of hyperthyroidism (135). However, they recommended  $^{131}\text{I}$  administration as soon as possible after dialysis and a delay in subsequent dialysis until the maximum  $^{131}\text{I}$  uptake has occurred in the thyroid. The radiation dose to the technician in the dialysis unit should be monitored, and the patient should undergo dialysis in a private room. Equipment and fluid disposed from the dialysis unit should be monitored by radiation safety personnel, but we did not find any contamination in a patient treated for thyroid cancer (136).

### CONCLUSION

The causes of thyrotoxicosis have been described, and the treatment of syndromes with increased trapping of iodine has been discussed. There are 3 frequently used therapies: antithyroid medications, thyroidectomy, and  $^{131}\text{I}$  treatment. The benefits of each and the potential side effects have been detailed.  $^{131}\text{I}$  treatment is cost-effective, safe, and reliable, and its application has been described in detail.

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