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be approximated by decreasing the upper limit of the nonpregnant reference range by 0.5 mIU/L (~4.0 mIU/L) and the lower limit by 0.4 mIU/L (~0.1 mIU/L). However, it is important to recognize that the normal TSH range in pregnancy for the second and third trimesters is not significantly different from the nonpregnancy ref erence range. Therefore, when caring for LT4-replaced women with hypothyroidism, thyroid function should be evaluated immediately after pregnancy is confirmed and every 4 weeks during the first half of the pregnancy, with less frequent testing after 20 weeks' gestation (every 6–8 weeks depending on whether LT4 dose adjustment is ongoing). The increment of LT4 dosage increase depends upon the etiology of hypothyroidism, with athyreotic women requiring more (~45%) than those with Hashimoto's who may have some residual thyroid function. Women should increase LT4 from once-daily dosing to nine doses per week as soon as pregnancy is confirmed to anticipate this change. Thereafter, dosage should be closely moni tored with a goal TSH in the lower half of the trimester-specific normative range, if available, or <2.5 mIU/L, which allows for reserve if additional LT4 dosage increases are required as pregnancy progresses. After delivery, LT4 doses typically return to prepreg nancy levels. Pregnant women should be counseled to separate ingestion of prenatal vitamins and iron supplements from LT4.

PART 12 Endocrinology and Metabolism Elderly patients may require 20% less thyroxine than younger patients. In the elderly, especially patients with known coronary artery disease, the starting dose of LT4 is 12.5–25 µg/d with similar increments every 2–3 months until TSH is normalized. In some patients, it may be impossible to achieve full replacement despite optimal antianginal treatment. Emergency surgery is generally safe in patients with untreated hypothyroidism, although routine sur gery in a hypothyroid patient should be deferred until euthyroidism is achieved. Myxedema coma still has a 20–40% mortality rate, despite inten sive treatment, and outcomes are independent of the T4 and TSH levels. Clinical manifestations include reduced level of conscious ness, sometimes associated with seizures, as well as the other features of hypothyroidism (Table 395-3). Hypothermia can reach 23°C (74°F). There may be a history of treated hypothyroidism with poor compliance, or the patient may be previously undiagnosed.

Myxedema coma almost always occurs in the elderly and is usu ally precipitated by factors that impair respiration, such as drugs (especially sedatives, anesthetics, and antidepressants), pneumo nia, congestive heart failure, myocardial infarction, gastrointestinal bleeding, or cerebrovascular accidents. Sepsis should also be sus pected. Exposure to cold may also be a risk factor. Hypoventilation, leading to hypoxia and hypercapnia, plays a major role in pathogen esis; hypoglycemia and dilutional hyponatremia also contribute to the development of myxedema coma. LT4 can initially be administered as a single IV bolus of 200– 400 µg, which serves as a loading dose, followed by a daily oral dose of 1.6 µg/kg per d, reduced by 25% if administered IV. If a suitable IV preparation is not available, the same initial dose of LT4 can be given by nasogastric tube (although absorption may be impaired in myxedema). Because T4 → T3 conversion is impaired in myxedema coma, there is a rationale for adding liothyronine (T3) intravenously or via nasogastric tube to LT4 treatment, although excess liothyro nine has the potential to provoke arrhythmias. An initial loading dose of 5–20 µg liothyronine should be followed by 2.5–10 µg every 8 h, with lower doses chosen for smaller or older patients and those at cardiovascular risk. Supportive therapy should be provided to correct any associated metabolic disturbances. External warming is indicated only if the temperature is <30°C, as it can result in cardiovascular collapse (Chap. 477). Space blankets should be used to prevent further heat loss. Parenteral hydrocortisone (50 mg every 6 h) should be administered because there is impaired adrenal reserve in pro found hypothyroidism. Any precipitating factors should be treated, including the early use of broad-spectrum antibiotics, pending the exclusion of infection. Ventilatory support with regular blood gas analysis is usually needed during the first 48 h. Hypertonic saline

or IV glucose may be needed if there is severe hyponatremia or hypoglycemia; hypotonic IV fluids should be avoided because they may exacerbate water retention secondary to reduced renal perfu sion and inappropriate vasopressin secretion. The metabolism of most medications is impaired, and sedatives should be avoided if possible or used in reduced doses. Medication blood levels should be monitored, when available, to guide dosage. ■ ■FURTHER READING Biondi B et al: Subclinical hypothyroidism in older individuals. Lancet Diabetes Endocrinol 10:129, 2022. Chaker L et al: Hypothyroidism. Nature Rev Dis Primers 8:30, 2022. Hegedüs L et al: Primary hypothyroidism and quality of life. Nature Rev Endocrinol 18:230, 2022. Jonklaas J et al: Guidelines for the treatment of hypothyroidism: Pre pared by the American Thyroid Association Task Force on thyroid hormone replacement. Thyroid 24:1670, 2014. Lee SY et al: Assessment and treatment of thyroid disorders in preg nancy and the postpartum period. Nat Rev Endocrinol 18:158, 2022. van Trotsenburg P et al: Congenital hypothyroidism: A 2020-2021 consensus guidelines update-an ENDO-European reference network initiative endorsed by the European Society for Pediatric Endocrinol ogy and the European Society for Endocrinology. Thyroid 31:387, 2021.

Hyperthyroidism and

Other Causes of

Thyrotoxicosis Anthony P. Weetman, Susan J. Mandel,

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THYROTOXICOSIS Thyrotoxicosis is defined as the state of thyroid hormone excess and is not synonymous with hyperthyroidism, which is the result of excessive thyroid function. However, the

major etiologies of thyrotoxicosis are hyperthyroidism caused by Graves' disease, toxic multinodular goiter (MNG), and toxic adenomas. Other causes are listed in Table 396-1. ■ ■GRAVES' DISEASE Epidemiology Graves' disease accounts for 60–80% of thyro toxicosis. The prevalence varies among populations, reflecting genetic factors and iodine intake (high iodine intake is associated with an increased prevalence of Graves' disease). Graves' disease occurs in up to 2% of women but is one-tenth as frequent in men. The disorder rarely begins before adolescence and typically occurs between 20 and 50 years of age; it also occurs in the elderly. Pathogenesis As in autoimmune hypothyroidism, a combina tion of environmental and genetic factors, including polymorphisms in HLA-DR, the immunoregulatory genes CTLA-4, CD25, CD40, PTPN22, FCRL3, and CD226, as well as the gene encoding the thyroidstimulating hormone (TSH) receptor (TSH-R), contributes to Graves' disease susceptibility. The concordance for Graves' disease in monozy gotic twins is 20–30%, compared to <5% in dizygotic twins. Indirect evidence suggests that stress is an important environmental factor, presumably operating through neuroendocrine effects on the immune system. Smoking is a moderate risk factor for Graves' disease and a major risk factor for the development of ophthalmopathy. Sudden increases in iodine intake may precipitate Graves' disease, and there is

TABLE 396-1 Causes of Thyrotoxicosis Primary Hyperthyroidism Graves' disease Toxic multinodular goiter Toxic adenoma Functioning thyroid carcinoma metastases Activating mutation of the TSH receptor Activating mutation of GSa (McCune-Albright syndrome) Struma ovarii Drugs: iodine excess (Jod-Basedow phenomenon) Thyrotoxicosis without Hyperthyroidism Subacute thyroiditis Silent thyroiditis Other causes of thyroid destruction: drugs (amiodarone, cytokines, tyrosine kinase inhibitors, immune checkpoint inhibitors), radiation, infarction of adenoma Ingestion of excess thyroid hormone (thyrotoxicosis factitia) or thyroid tissue Secondary Hyperthyroidism TSH-secreting pituitary adenoma Thyroid hormone resistance syndrome: occasional patients may have features of thyrotoxicosis Chorionic gonadotropin-secreting tumorsa Gestational thyrotoxicosisa aCirculating TSH levels are low in these forms of secondary hyperthyroidism. Abbreviation: TSH, thyroid-stimulating hormone. a threefold increase in the occurrence of Graves' disease in the post partum period. Graves' disease may occur during the immune recon stitution phase after highly active antiretroviral therapy (HAART) or alemtuzumab treatment and following treatment with immune check point inhibitors (e.g., nivolumab, pembrolizumab). The hyperthyroidism of Graves' disease is caused by thyroidstimulating immunoglobulins (TSIs) that are synthesized by lympho cytes in the thyroid gland as well as in bone marrow and lymph nodes. Such antibodies can be detected by bioassays or by using the more widely available immunoassays (TSH receptor antibodies [TRAb]) that measure whether the patient's serum contains an antibody that can dis place either labeled TSH or a monoclonal TSH receptor antibody from the TSH receptor. The presence of TRAb in a patient with thyrotoxi cosis implies the existence of TSI, and these assays are useful in moni toring pregnant Graves' patients in whom high levels of TSI can cross the placenta and cause neonatal thyrotoxicosis. Other thyroid autoim mune responses, similar to those in autoimmune hypothyroidism (see above), occur concurrently in patients with Graves' disease. In particu lar, thyroid peroxidase (TPO) and thyroglobulin (Tg) antibodies occur in up to 80% of cases. Because the coexisting lymphocytic thyroiditis can also affect thyroid function, there is no direct correlation between the level of TSI and thyroid hormone levels in Graves' disease. Cytokines appear to play a major role in thyroid-associated ophthal mopathy. There is infiltration of the extraocular muscles by activated T cells; the release of cytokines such as interferon γ (IFN-γ), tumor necrosis factor (TNF), and interleukin 1 (IL-1) results in fibroblast activation and increased

synthesis of glycosaminoglycans that trap water, thereby leading to characteristic muscle swelling. Late in the disease, there is irreversible fibrosis of the muscles. Increased fat is an additional cause of retrobulbar tissue expansion. The increase in intra orbital pressure can lead to proptosis, diplopia, and optic neuropathy. Although the pathogenesis of thyroid-associated ophthalmopathy is incompletely understood, the TSH-R is a thyroid autoantigen and is expressed in orbital tissues. In addition, aberrant signaling via insulinlike growth factor 1 receptors (IGF-1R) on orbital fibroblasts has also been implicated. These mechanisms are the basis for new monoclonal antibody treatments (e.g., teprotumumab) that reduce the levels of TSH-R/IGF-1R complexes and attenuate signaling. Clinical Manifestations Signs and symptoms include features that are common to any cause of thyrotoxicosis (Table 396-2) as well

TABLE 396-2 Signs and Symptoms of Thyrotoxicosis (Descending Order of Frequency) SYMPTOMS SIGNSa Hyperactivity, irritability, dysphoria Heat intolerance and sweating Palpitations Fatigue and weakness Weight loss with increased appetite Diarrhea Polyuria Oligomenorrhea, loss of libido Tachycardia; atrial fibrillation in the elderly Tremor Goiter Warm, moist skin Muscle weakness, proximal myopathy Lid retraction or lag Gynecomastia Hyperthyroidism and Other Causes of Thyrotoxicosis
CHAPTER 396 aExcludes the signs of ophthalmopathy and dermopathy specific for Graves' disease.
as those specific for Graves' disease. The clinical presentation depends on the severity of thyrotoxicosis, the duration of disease, individual susceptibility to excess thyroid hormone, and the patient's age. In the elderly, features of thyrotoxicosis may be subtle or masked, and patients may present mainly with fatigue and weight loss, a condition known as apathetic thyrotoxicosis. Thyrotoxicosis may cause unexplained weight loss, despite an enhanced appetite, due to the increased metabolic rate. Weight gain occurs in 5% of patients, however, because of increased food intake. Other prominent features include hyperactivity, nervousness, and irritability, ultimately leading to a sense of easy fatigability in some patients. Insomnia and impaired concentration are common; apathetic thyrotoxicosis may be mistaken for depression in the elderly. Fine tremor is a frequent finding, best elicited by having patients stretch out their fingers while feeling the fingertips with the palm. Common neurologic manifestations include hyperreflexia, muscle wasting, and proximal myopathy without fasciculation. Chorea is rare. Thyro toxicosis is sometimes associated with a form of hypokalemic periodic paralysis; this disorder is particularly common in Asian males with thyrotoxicosis, but it occurs in other ethnic groups as well. The most common cardiovascular manifestation is sinus tachycar dia, often associated with palpitations, occasionally caused by supra ventricular tachycardia. The high cardiac output produces a bounding pulse, widened pulse pressure, and an aortic systolic murmur and can lead to worsening of angina or heart failure in the elderly or those with preexisting heart disease. Atrial fibrillation is more common in patients

> 50 years of age. Treatment of the thyrotoxic state alone converts atrial fibrillation to normal sinus rhythm in up to 75% of patients without an underlying cardiac problem. The skin is usually warm and moist, and the patient may complain of sweating and heat intolerance, particularly during warm weather. Palmar erythema, onycholysis, and, less commonly, pruritus, urticaria, and diffuse hyperpigmentation may be evident. Hair texture may become fine, and

> diffuse alopecia occurs in up to 40% of patients, per sisting for months after restoration of euthyroidism. Gastrointestinal transit time is decreased, leading to increased stool frequency, often with diarrhea and occasionally mild steatorrhea. Women frequently experience oligomenorrhea or amenorrhea; in men, there may be impaired sexual function and, rarely, gynecomastia. The direct effect of thyroid hormones on bone resorption leads to osteopenia in longstanding thyrotoxicosis; mild hypercalcemia occurs in up to 20% of patients, but hypercalciuria is more common. There is a small increase in fracture rate in patients with a previous history of thyrotoxicosis. In Graves' disease, the thyroid is usually diffusely enlarged to two to three times its normal size. The consistency is firm, but not nodular. There may be a thrill or bruit, best detected at the inferolateral margins of the thyroid lobes, due to the increased vascularity of the gland and the hyperdynamic circulation. Lid retraction, causing a staring appearance, can occur in any form of thyrotoxicosis and is the result of sympathetic overactivity. However, Graves' disease is associated with specific eye signs that comprise Graves' ophthalmopathy (Fig. 396-1A). This condition is also called thyroid eye disease (TED) because it occurs in the absence

PART 12 Endocrinology and Metabolism A B C FIGURE 396-1 Features of Graves' disease. A. Ophthalmopathy in Graves' disease; lid retraction, periorbital edema, conjunctival injection, and proptosis are marked. B. Thyroid dermopathy over the lateral aspects of the shins. C. Thyroid acropachy. of hyperthyroidism in 10% of patients. Most of these individuals have autoimmune hypothyroidism or thyroid antibodies. The onset of Graves' ophthalmopathy occurs within the year before or after the diagnosis of thyrotoxicosis in 75% of patients but can sometimes precede or follow thyrotoxicosis by several years, accounting for some cases of euthyroid ophthalmopathy. About one-third of patients with Graves' disease have clinical evi dence of ophthalmopathy. However, the enlarged extraocular muscles typical of the disease, and other subtle features, can be detected in most patients when investigated by ultrasound or computed tomography (CT) imaging of the orbits. Unilateral signs are found in up to 10% of ophthalmopathy patients. The earliest manifestations of ophthalmopa thy are usually a sensation of grittiness, eye discomfort, and excess tearing. About one-third of patients have proptosis, best detected by visualization of the sclera between the lower border of the iris and the lower eyelid, with the eyes in the primary position. Proptosis can be measured using an exophthalmometer. In severe cases, proptosis may cause corneal exposure and damage, especially if the lids fail to close during sleep. Periorbital edema, scleral injection, and chemosis are also frequent. In 5–10% of patients, the muscle swelling is so severe that diplopia results, typically, but not exclusively, when the patient looks up and laterally. The most serious manifestation is compression of the optic nerve at the apex of the orbit, leading to papilledema; peripheral field defects; and, if left untreated, permanent loss of vision. The "NO SPECS" scoring system to evaluate ophthalmopathy is an acronym derived from the following changes: 0 = No signs or symptoms 1 = Only signs (lid retraction or lag), no symptoms 2 = Soft tissue involvement (periorbital edema) 3 = Proptosis (>22 mm) 4 = Extraocular muscle involvement (diplopia) 5 = Corneal involvement 6 = Sight loss Although useful as a mnemonic, the NO SPECS scheme is inad equate to describe the eye disease fully, and patients do not necessarily progress from one class to another; alternative scoring systems (e.g., the EUGOGO system

developed by the European Group on Graves' Orbitopathy) that assess disease activity are preferable for monitor ing and treatment purposes. When Graves' eye disease is active and

moderate to severe, evaluation and management with an ophthal mologist is indicated, and objective measurements are needed, such as lid-fissure width; corneal staining with fluorescein; evaluation of extraocular muscle function (e.g., Hess chart), intraocular pressure and visual fields, acuity, and color vision; and orbital imaging with CT or magnetic resonance imaging (MRI). Thyroid dermopathy occurs in <5% of patients with Graves' disease (Fig. 396-1B), almost always in the presence of moderate or severe ophthalmopathy. Although most frequent over the anterior and lateral aspects of the lower leg (hence the term pretibial myxedema), skin changes can occur at other sites, particularly after trauma. The typical lesion is a noninflamed, indurated plaque with a deep pink or purple color and an "orange skin" appearance. Nodular involvement can occur, and the condition can rarely extend over the whole lower leg and foot, mimicking elephantiasis. Thyroid acropachy refers to a form of clubbing found in <1% of patients with Graves' disease (Fig. 396-1C). It is so strongly associated with thyroid dermopathy that an alternative cause of clubbing should be sought in a Graves' patient without coinci dent skin and orbital involvement. Ophthalmopathy, dermopathy, and acropachy have declined in incidence, probably due to better recogni tion and prompt treatment of the underlying thyroid disease. Laboratory Evaluation Investigations used to determine the existence and cause of thyrotoxicosis are summarized in Fig. 396-2. In Graves' disease, the TSH level is suppressed, and total and unbound thyroid hormone levels are increased. In 2–5% of patients (and more in areas of borderline iodine intake), only T3 is increased (T3 toxicosis). The converse state of T4 toxicosis, with elevated total and unbound T4 and normal T3 levels, is occasionally seen when hyperthyroidism is induced by excess iodine, providing surplus substrate for thyroid hormone synthesis. Measurement of TRAb is also useful. Associated abnormalities that may cause diagnostic confusion in thyrotoxicosis include elevation of bilirubin, liver enzymes, and ferritin. Microcytic anemia and thrombocytopenia may occur. Differential Diagnosis Diagnosis of Graves' disease is straightfor ward in a patient with biochemically confirmed thyrotoxicosis, diffuse goiter on palpation, ophthalmopathy, and often a personal or family history of autoimmune disorders. TRAb measurement is usually used to confirm the diagnosis of Graves' disease in patients with thyrotoxi cosis who lack these features, but the diagnosis can also be established by a radionuclide (99mTc, 123I, or 131I) scan and uptake of the thyroid, which will distinguish the diffuse, high uptake of Graves' disease from destructive thyroiditis, ectopic thyroid tissue, and factitious thyrotoxi cosis, as well as diagnose a toxic adenoma or toxic MNG. Alternatively, color-flow Doppler ultrasonography distinguishes between hyperthy roidism (with increased blood flow) and destructive thyroiditis and avoids using radioactivity. In secondary hyperthyroidism due to a TSH-secreting pituitary tumor, there is also a diffuse goiter. The pres ence of a nonsuppressed TSH level and the finding of a pituitary tumor on CT or MRI scan suggest this diagnosis. Clinical features of thyrotoxicosis can mimic certain aspects of other disorders, including panic attacks, mania, pheochromocytoma, and weight loss associated with malignancy. The diagnosis of thyrotoxi cosis can be easily excluded if the TSH and unbound T4 and T3 levels are normal. A normal TSH also excludes Graves' disease as a cause of diffuse goiter. Clinical Course Clinical features generally worsen without treat ment; mortality was 10–30% before the introduction of satisfactory therapy. Some patients with mild Graves' disease experience spontane ous relapses and remissions. Rarely, there may be fluctuation between hypo- and hyperthyroidism due to changes in the functional activity of TSH-R antibodies. About 15% of patients who enter remission after treatment develop hypothyroidism 10–15 years later because of the destructive

autoimmune process. The clinical course of ophthalmopathy does not follow that of the thyroid disease, although thyroid dysfunction can worsen eye signs. Ophthalmopathy typically worsens over the initial 3–6 months, fol lowed by a plateau phase over the next 12–18 months, and then some

Measure TSH, unbound T4 TSH low, unbound T4 normal TSH and unbound T4 normal TSH low, unbound T4 high Measure unbound T3 Primary thyrotoxicosis High T3 toxicosis Subclinical hyperthyroidism Features of Graves' diseasea? Yes No Graves' disease Multinodular goiter or toxic adenomab? Yes No Toxic nodular hyperthyroidism Low radionuclide uptake? Yes No Destructive thyroiditis, iodine excess or excess thyroid hormone Rule out other causes including stimulation by chorionic gonadotropin FIGURE 396-2 Evaluation of thyrotoxicosis. aDiffuse goiter, positive thyroid peroxidase (TPO) antibodies or thyroid-stimulating hormone (TSH) receptor antibody (TRAb), ophthalmopathy, dermopathy. bCan be confirmed by radionuclide scan. spontaneous improvement, particularly in the soft tissue changes. However, the course is more fulminant in up to 5% of patients, requir ing intervention in the acute phase if there is optic nerve compression or corneal ulceration. Diplopia may appear late in the disease due to fibrosis of the extraocular muscles. Radioiodine treatment for hyper thyroidism worsens the eye disease in a small proportion of patients (especially smokers). Antithyroid drugs and surgery have no adverse effects on the clinical course of ophthalmopathy. Thyroid dermopathy, when it occurs, usually appears 1–2 years after the development of Graves' hyperthyroidism; it may improve spontaneously. TREATMENT Graves' Disease The hyperthyroidism of Graves' disease is treated by reducing thy roid hormone synthesis, using an antithyroid drug, or reducing the amount of thyroid tissue with radioiodine (131I) treatment or by thyroidectomy. Antithyroid drugs are the predominant initial therapy in many centers in Europe, Latin America, and Japan, whereas radioiodine is more often the first line of treatment in North America. These differences reflect the fact that no single approach is optimal and that patients may require multiple treat ments to achieve remission. The main antithyroid drugs are thionamides: propylthiouracil, carbimazole (not available in the United States), and the active metabolite of the latter, methimazole. All inhibit the function of TPO, reducing oxidation and organification of iodide. These drugs also reduce thyroid antibody levels by mechanisms that remain unclear, and they appear to enhance spontaneous rates of remission. Propylthiouracil inhibits deiodination of T4 → T3. However, this effect is of minor benefit, except in the most severe thyrotoxicosis, and is offset by the much shorter half-life of this drug (90 min) compared to methimazole (6 h). Due to the hepatotoxicity of pro pylthiouracil, the U.S. Food and Drug Administration (FDA) has limited indications for its use to the first trimester of pregnancy,

TSH normal or increased, high unbound T4 TSH-secreting pituitary adenoma or thyroid hormone resistance syndrome Normal Hyperthyroidism and Other Causes of Thyrotoxicosis
 No further tests Follow up in 6–12 weeks the treatment of thyroid storm, and patients with minor adverse reactions to methimazole. If propylthiouracil is used, monitoring of liver function tests is recommended. There are many variations of antithyroid drug regimens. The initial dose of carbimazole or methimazole is usually 10–20 mg every 12 h, but once-daily dosing is possible after euthyroidism is restored. Propylthiouracil is given at a dose of 100–200 mg every 6–8 h, and divided doses are usually given throughout the course. Lower doses of each drug may suffice in areas of low iodine intake. The starting dose of an antithyroid drug can be gradually reduced (titration regimen) as thyrotoxicosis improves. Less commonly, high doses may be given combined with levothyroxine (LT4) supplementation (block-replace regimen) to avoid drug-induced

hypothyroidism. The titration regimen is often preferred to mini mize the dose of antithyroid drug and provide an index of treatment response. Thyroid function tests and clinical manifestations are reviewed 4–6 weeks after starting treatment, and the dose is titrated based on unbound T4 levels. Most patients do not achieve euthyroidism until 6–8 weeks after treatment is initiated. TSH levels often remain suppressed for several months and therefore do not provide a sen sitive index of treatment response. The usual daily maintenance doses of antithyroid drugs in the titration regimen are 2.5–10 mg of carbimazole or methimazole and 50–100 mg of propylthiouracil. In the block-replace regimen, the initial dose of antithyroid drug is held constant, and the dose of LT4 is adjusted to maintain normal unbound T4 levels. When TSH suppression is alleviated, TSH levels can also be used to monitor therapy. Maximum remission rates (30–60%) are achieved by 12–18 months for the titration regimen and are higher in patients in whom TRAb levels are no longer detected than in those with TRAb persistence. For unclear reasons, remission rates appear to vary in different geographic regions. Younger patients, males, smokers, and patients with a history of allergy, severe hyperthyroidism, or large goiters are most likely to relapse when treatment stops, as are those with enduring TRAb, but outcomes are difficult to predict. All patients

should be followed closely for relapse during the first year after treatment and at least annually thereafter. Prolonged treatment for up to 10 years with small doses of an antithyroid drug has been used as an alternative to ablative therapies following relapse.

The common minor side effects of antithyroid drugs are rash, urticaria, fever, and arthralgia (1–5% of patients). These may resolve spontaneously or after substituting an alternative antithy roid drug; rashes may respond to an antihistamine. Rare but major side effects include hepatitis (especially with propylthiouracil; avoid use in children) and cholestasis (methimazole and carbimazole); vasculitis; and, most important, agranulocytosis (<1%). It is essen tial that antithyroid drugs are stopped and not restarted if a patient develops major side effects. Written instructions should be pro vided regarding the symptoms of possible agranulocytosis (e.g., sore throat, fever, mouth ulcers) and the need to stop treatment pending an urgent complete blood count to confirm that agranulocytosis is not present. Management of agranulocytosis is described in Chap. 107. It is not useful to monitor blood counts prospectively, because the onset of agranulocytosis is idiosyncratic and abrupt. PART 12 Endocrinology and Metabolism Propranolol (20–40 mg every 6 h) or longer-acting selective β1 receptor blockers such as atenolol may be helpful to control adren ergic symptoms, especially in the early stages before antithyroid drugs take effect. Beta blockers are also useful in patients with thy rotoxic periodic paralysis, pending correction of thyrotoxicosis. In consultation with a cardiologist or using a risk score like CHA2DS2VASc, anticoagulation should be considered in all patients with atrial fibrillation; the majority revert spontaneously to sinus rhythm with control of hyperthyroidism, and long-term anticoagulation is not usually needed. Decreased warfarin doses are required when patients are thyrotoxic. If digoxin is used, increased doses are often needed in the thyrotoxic state. Radioiodine causes progressive destruction of thyroid cells and can be used as initial treatment or for relapses after a trial of anti thyroid drugs. There is a small risk of thyrotoxic crisis (see below) after radioiodine, which can be minimized by pretreatment with antithyroid drugs for at least a month before treatment. Antecedent treatment with an antithyroid drug and a beta blocker should be considered for all elderly patients or for those with cardiac prob lems. Carbimazole or methimazole must be stopped 2–3 days before radioiodine administration to achieve optimum iodine uptake and can be restarted 3–7 days after radioiodine in those at risk of com plications from worsening thyrotoxicosis. Propylthiouracil

appears to have a prolonged radioprotective effect and should be stopped for a longer period before radioiodine is given, or a larger dose of radioiodine will be necessary. Efforts to calculate an optimal dose of radioiodine that achieves euthyroidism without a high incidence of relapse or progression to hypothyroidism have not been successful. Some patients inevitably relapse after a single dose because the biologic effects of radiation vary between individuals, and hypothyroidism cannot be uniformly avoided even using accurate dosimetry. A practical strategy is to give a fixed dose based on clinical features, such as the severity of thyrotoxicosis, the size of the goiter (larger goiters need a higher dosage) and the radioiodine uptake (higher uptake decreases the dosage needed). 131I dosage generally ranges between 370 MBq (10 mCi) and 555 MBq (15 mCi). Most authorities favor an approach aimed at thyroid ablation (as opposed to euthyroidism), given that LT4 replacement is straightforward and most patients ultimately prog ress to hypothyroidism over 5–10 years. Certain radiation safety precautions are necessary in the first few days after radioiodine treatment, but the exact guidelines vary depending on local protocols. In general, patients need to avoid close, prolonged contact with children and pregnant women for 5–7 days because of possible transmission of residual isotope and exposure to radiation emanating from the gland. Rarely, there may be mild pain due to radiation thyroiditis 1–2 weeks after treatment. Hyperthyroidism can persist for 2–3 months before radioiodine takes full effect. For this reason, β-adrenergic blockers or anti thyroid drugs, which can be restarted 5–7 days after radioiodine

administration, can be used to control symptoms during this inter val. Persistent hyperthyroidism can be treated with a second dose of radioiodine, usually 6 months after the first dose. The risk of hypothyroidism after radioiodine depends on the dosage but is at least 10–20% in the first year and 5% per year thereafter and 5% per year thereafter, with higher rates after ablative treatment. Patients should be informed of this possibility before treatment and require close follow-up during the first year followed by annual thyroid function testing. Pregnancy and breast-feeding are absolute contraindications to radioiodine treatment, but patients can conceive safely 6 months after treatment. The presence of ophthalmopathy, especially in smokers, requires caution. Prednisone, 0.2–0.5 mg/kg per d (depending on ophthalmopathy severity), at the time of radioiodine treatment, tapered over 6–12 weeks, may prevent exacerbation of ophthalmopathy, but radioiodine should generally be avoided in patients with active moderate-to-severe eye disease. Although many physicians avoid radioiodine in children and adolescents because of the potential risks of malignancy, others have advocated radioio dine use in older children. There is no overall increase in cancer risk after radioiodine. Patients may be advised that the risks are small enough to be indistinguishable from antithyroid drugs or surgery. Total or near-total thyroidectomy is an option for patients who relapse after antithyroid drugs and prefer this treatment to radio iodine. Some experts recommend surgery in young individuals, particularly when the goiter is very large. Careful control of thy rotoxicosis with antithyroid drugs, followed by potassium iodide (SSKI; 1–2 drops orally tid for 10 days), is needed prior to surgery to avoid thyrotoxic crisis and to reduce the vascularity of the gland. The major complications of surgery—bleeding, laryngeal edema, hypoparathyroidism, and damage to the recurrent laryngeal nerves—are unusual when the procedure is performed by highly experienced surgeons. Recurrence rates in the best series are <2%, but the rate of hypothyroidism is similar to that following radioio dine treatment, especially with the current trend away from subtotal thyroidectomy. Antithyroid drugs should be used to manage active Graves’ disease in pregnancy. Because transplacental passage of these drugs may produce fetal hypothyroidism and goiter if the maternal dose is excessive, maternal antithyroid dose titration should target serum free or total T4 levels at or just above the pregnancy reference

range. If available, propylthiouracil should be used until 14–16 weeks' gestation because of the risk of rare cases of methimazole/carbimazole embryopathy, including aplasia cutis and other defects, such as choanal atresia and tracheoesophageal fistulae. Because of the potential for teratogenic effects, antithyroid medication should be discontinued in any newly pregnant woman with Graves' disease who is euthyroid on a low dose of methimazole (<5–10 mg/d) or propylthiouracil (<100–200 mg/d), after evaluating recent thyroid function tests, disease history, goiter size, duration of therapy, and TRAb measurement. Following cessation, careful monitoring of maternal thyroid function tests is essential. On the other hand, for women at high risk of developing thyrotoxicosis if antithyroid drugs are discontinued (large goiter, requirement for higher antithyroid drug dosage, elevated TRAb), continued therapy is necessary, with propylthiouracil (if available) administration in the first trimester. Because of its rare association with hepatotoxicity, propylthiouracil should be limited to the first trimester and then maternal therapy should be converted to methimazole (or carbimazole) at a ratio of 15–20 mg of propylthiouracil to 1 mg of methimazole. It is often possible to stop treatment in the last trimester because TSI tend to decline in pregnancy. Nonetheless, the transplacental transfer of these antibodies, if present, at levels three times higher than the normative range may rarely cause fetal or neonatal thyrotoxicosis. Poor intrauterine growth, a fetal heart rate of >160 beats/min, advanced bone age, fetal goiter, and high levels of maternal TSI after 26 weeks' gestation may herald this complication. Antithyroid drugs given to the mother can be used to treat the fetus and may be needed for 1–3 months after delivery, until the maternal antibodies

disappear from the baby's circulation. The postpartum period is a time of major risk for relapse of Graves' disease. Breast-feeding is safe with low doses of antithyroid drugs. Graves' disease in children is usually managed initially with methimazole or carbimazole (avoid propylthiouracil), often given as a course of the titration regi men for at least 3 years. Surgery or radioiodine may be indicated for severe or relapsing disease. Thyrotoxic crisis, or thyroid storm, is rare and presents as a life-threatening exacerbation of hyperthyroidism, accompanied by fever, delirium, seizures, coma, vomiting, diarrhea, and jaundice. The mortality rate due to cardiac failure, arrhythmia, or hyper thermia is high (4–17%) even with treatment. Thyrotoxic crisis is usually precipitated by acute illness (e.g., stroke, infection, trauma, diabetic ketoacidosis), surgery (especially on the thyroid), or radio iodine treatment of a patient with partially treated or untreated hyperthyroidism. Management requires intensive monitoring and supportive care, identification and treatment of the precipitating cause, and measures that reduce thyroid hormone synthesis. Large doses of propylthiouracil (500–1000 mg loading dose and 250 mg every 4 h) should be given orally or by nasogastric tube or per rec tum; the drug's inhibitory action on T4 → T3 conversion makes it the antithyroid drug of choice. If not available, methimazole can be used in doses of 20 mg every 6 h. One hour after the first dose of propylthiouracil or methimazole, stable iodide (5 drops SSKI every 6 h) is given to block thyroid hormone synthesis via the WolffChaikoff effect (the delay allows the antithyroid drug to prevent the excess iodine from being incorporated into new hormone). Propranolol should also be given to reduce tachycardia and other adrenergic manifestations (60–80 mg PO every 4 h, or 2 mg IV every 4 h). Although other β-adrenergic blockers can be used, high doses of propranolol decrease T4 → T3 conversion, and the doses can be easily adjusted. Caution is needed to avoid acute negative inotropic effects, but controlling the heart rate is important, as some patients develop a form of high-output heart failure. Short-acting IV esmolol can be used to decrease heart rate while monitoring for signs of heart failure. Additional therapeutic measures include glucocorticoids (e.g., hydrocortisone 300 mg IV bolus, then 100 mg every 8 h), antibiotics if

infection is present, cholestyramine to sequester thyroid hormones, cooling, oxygen, and IV fluids. Mild ophthalmopathy requires no active treatment, because there is usually spontaneous improvement. General measures include meticulous control of thyroid hormone levels, cessation of smoking, and an explanation of the natural history of ophthalmopathy. Dis comfort can be relieved with artificial tears (e.g., hypromellose 0.3% or carbomer 0.2% ophthalmic gel), paraffin-based eye ointment, and the use of dark glasses with side frames. Periorbital edema may respond to a more upright sleeping position or a diuretic. Corneal exposure during sleep can be avoided by using patches or taping the eyelids shut. Minor degrees of diplopia improve with prisms fitted to spectacles. Some authorities also advocate selenium 100 µg bid. Moderate-to-severe ophthalmopathy, in which the eye disease has sufficient impact on daily life to justify the risks of treatment, is usually treated with IV methylprednisolone (e.g., 500 mg of methylprednisolone once weekly for 6 weeks, then 250 mg once weekly for 6 weeks). This is preferable to oral glucocorticoids. A poor response at 6 weeks generally indicates the need for alternative treatment. Once the eye disease has stabilized, surgery may be indi cated for relief of diplopia and correction of appearance. External beam radiotherapy of the orbits has been used for many years, but the efficacy of this therapy remains unclear, and it is best reserved for those who are not responsive to glucocorticoid therapy. Tepro tumumab, a monoclonal antibody inhibitor of the IGF-1 receptor, improves proptosis, diplopia, clinical activity score, and quality of life and is recommended as first-line treatment in patients with active moderate-to-severe ophthalmopathy with significant pro ptosis or diplopia, but use may be limited by availability and cost. Relapse rates are similar to glucocorticoids (30%). Rituximab and tocilizumab are other monoclonal antibodies that have been used as second-line treatment after glucocorticoids. Sight-threatening

ophthalmopathy due to optic nerve compression or corneal damage is an emergency that requires immediate high-dose IV glucocorti coids (e.g., methylprednisolone 500–1000 mg on alternate days). If there is a poor response after 2 weeks, surgical orbital decom pression should be considered by removing bone from the medial and inferior orbital wall, thereby allowing displacement of fat and swollen extraocular muscles. In addition to nerve decompression, proptosis recedes an average of 5 mm, but there may be residual or even worsened diplopia.

Thyroid dermopathy does not usually require treatment, but it can cause cosmetic problems or interfere with the fit of shoes. Surgical removal is not indicated. If necessary, treatment consists of topical, high-potency glucocorticoid ointment under an occlusive dressing or compression dressing. Teprotumumab has been benefi cial in some cases. Hyperthyroidism and Other Causes of Thyrotoxicosis

CHAPTER 396 ■ ■OTHER CAUSES OF THYROTOXICOSIS Destructive thyroiditis (subacute or silent thyroiditis) typically presents with a short thyrotoxic phase due to the release of preformed thyroid hormones and catabolism of Tg (see “Subacute Thyroiditis,” below). True hyperthyroidism is absent, as demonstrated by a low radionuclide uptake. Circulating Tg levels are typically increased. Other causes of thyrotoxicosis with low or absent thyroid radionuclide uptake include thyrotoxicosis factitia, iodine excess, and, rarely, ectopic thyroid tissue, particularly teratomas of the ovary (struma ovarii) and functional metastatic follicular carcinoma. Whole-body radionuclide studies can demonstrate ectopic thyroid tissue, and thyrotoxicosis factitia can be distinguished from destructive thyroiditis by the clinical features and low levels of Tg. Amiodarone treatment is associated with thyrotoxico sis in up to 10% of patients, particularly in areas of low iodine intake (see below). TSH-secreting pituitary adenoma is a rare cause of thyrotoxicosis. It is characterized

by the presence of an inappropriately normal or increased TSH level in a patient with hyperthyroidism, diffuse goiter, and elevated T4 and T3 levels (Chap. 392). Elevated levels of the α subunit of TSH, released by the TSH-secreting adenoma, support this diagnosis, which can be confirmed by demonstrating the pituitary tumor on MRI or CT scan. A combination of transsphenoidal surgery, sella irradiation, and octreotide may be required to normalize TSH, because many of these tumors are large and locally invasive at the time of diagnosis. Radioiodine or antithyroid drugs can be used to control thyrotoxicosis. Thyrotoxicosis caused by toxic MNG and hyperfunctioning solitary nodules is discussed below (Chap. 396). THYROIDITIS There are several classification systems to describe the clinical syn dromes of thyroiditis. One is based on the onset and duration of disease (Table 396-3); others are based on the absence or presence of pain. ■ ■ACUTE THYROIDITIS Acute thyroiditis is rare and due to suppurative infection of the thyroid. In children and young adults, the most common cause is the presence of a piriform sinus, a remnant of the fourth branchial pouch that con nects the oropharynx with the thyroid. Such sinuses are predominantly left-sided. A long-standing goiter and degeneration in a thyroid malig nancy are risk factors in the elderly. The patient presents with thyroid pain, often referred to the throat or ears, and a small, tender goiter that may be asymmetric. Fever, dysphagia, and erythema over the thyroid are common, as are systemic symptoms of a febrile illness and lymphadenopathy. The differential diagnosis of thyroid pain includes subacute or, rarely, chronic thyroiditis; hemorrhage into a cyst; malignancy includ ing lymphoma; and, rarely, amiodarone-induced thyroiditis or amyloi dosis. However, the abrupt presentation and clinical features of acute thyroiditis rarely cause confusion. The erythrocyte sedimentation rate (ESR) and white cell count are usually increased, but thyroid func tion is generally normal. Fine-needle aspiration (FNA) biopsy shows infiltration by polymorphonuclear leukocytes; culture of the sample

TABLE 396-3 Causes of Thyroiditis Acute Bacterial infection: especially Staphylococcus, Streptococcus, and Enterobacter Fungal infection: Aspergillus, Candida, Coccidioides, Histoplasma, and Pneumocystis Radiation thyroiditis after 131I treatment Amiodarone (may also be subacute or chronic) Subacute Viral (or granulomatous) thyroiditis Silent thyroiditis (including postpartum thyroiditis) PART 12 Endocrinology and Metabolism Mycobacterial infection Drug-induced (interferon, amiodarone, tyrosine kinase inhibitors, immune checkpoint inhibitors) Chronic Autoimmunity: focal thyroiditis, Hashimoto’s thyroiditis, atrophic thyroiditis FIGURE 396-3 Clinical course of subacute thyroiditis. The release of thyroid hormones is initially associated with a thyrotoxic phase and suppressed thyroidstimulating hormone (TSH). A hypothyroid phase then ensues, with low T4 and TSH levels that are initially low but gradually increase. During the recovery phase, increased TSH levels combined with resolution of thyroid follicular injury lead to normalization of thyroid function, often several months after the beginning of the illness. ESR, erythrocyte sedimentation rate; UT4, free or unbound T4. can identify the organism. Caution is needed in immunocompromised patients as fungal, mycobacterial, or Pneumocystis thyroiditis can occur in this setting. Antibiotic treatment is guided initially by Gram stain and, subsequently, by cultures of the FNA biopsy. Surgery may be needed to drain an abscess, which can be localized by CT scan or ultrasound. Tracheal obstruction, septicemia, retropharyngeal abscess, mediastinitis, and jugular venous thrombosis may complicate acute thyroiditis but are uncommon with prompt use of antibiotics. Riedel’s thyroiditis Parasitic thyroiditis: echinococcosis, strongyloidiasis, cysticercosis Traumatic: after palpation ■ ■SUBACUTE THYROIDITIS This is also termed de Quervain’s thyroiditis, granulomatous thyroid itis, or viral thyroiditis. Many viruses have been implicated, including mumps, coxsackie, influenza, adenoviruses, and echoviruses. Subacute

thyroiditis may also occur with the SARS-CoV-2 illness or after receiv ing the COVID vaccine. The diagnosis may be overlooked because the symptoms can mimic pharyngitis. Attempts to identify the causative virus in an individual patient are often unsuccessful and do not influ ence management. The peak incidence occurs at 30–50 years, and women are affected three times more frequently than men. Pathophysiology The thyroid shows a characteristic patchy inflammatory infiltrate with disruption of the thyroid follicles and multinucleated giant cells within some follicles. The follicular changes progress to granulomas accompanied by fibrosis. Finally, the thyroid returns to normal, usually several months after onset. During the ini tial phase of follicular destruction, there is release of Tg and thyroid hormones, leading to increased circulating T4 and T3 and suppres sion of TSH (Fig. 396-3). During this destructive phase, radioactive iodine uptake is low or undetectable. After several weeks, the thyroid is depleted of stored thyroid hormone and a phase of hypothyroid ism typically occurs, with low unbound T4 (and sometimes T3) and moderately increased TSH levels. Radioactive iodine uptake returns to normal or is even increased as a result of the rise in TSH. Finally, thy roid hormone and TSH levels return to normal as the disease subsides. Clinical Manifestations The patient usually presents with a pain ful and enlarged thyroid, sometimes accompanied by fever. There may be features of thyrotoxicosis or hypothyroidism, depending on the phase of the illness. Malaise and symptoms of an upper respiratory tract infec tion may precede the thyroid-related features by several weeks. In other patients, the onset is acute, severe, and without obvious antecedent. The patient typically complains of a sore throat, and examination reveals a small goiter that is exquisitely tender. Pain is often referred to the jaw or ear. Complete resolution is the usual outcome, but late-onset permanent hypothyroidism occurs in 15% of cases, particularly in those with coin cidental thyroid autoimmunity. A prolonged course over many months, with one or more relapses, occurs in a small percentage of patients.

ESR TSH

UT4

UT4 (pmol/L) ESR (mm/h) TSH (mU/L)

0.5

0.01

Time (weeks) Thyrotoxic Hypothyroid Recovery Clinical Phases Laboratory Evaluation As depicted in Fig. 396-3, thyroid func tion tests characteristically evolve through three distinct phases over about 6 months: (1) thyrotoxic phase, (2) hypothyroid phase, and (3) recovery phase. In the thyrotoxic phase, T4 and T3 levels are increased, reflecting their discharge from the damaged thyroid cells, and TSH is suppressed. The T4/T3 ratio is lower than in Graves’ or thyroid auton omy, in which T3 is often disproportionately increased. The diagnosis is confirmed by a high ESR and low uptake of radioiodine (<5%) or 99mTc pertechnetate (as compared to salivary gland pertechnetate con centration). The white blood cell count may be increased, and thyroid antibodies are negative. If the diagnosis is in doubt, FNA biopsy may be useful, particularly to distinguish unilateral involvement from bleeding into a cyst or neoplasm. TREATMENT Subacute Thyroiditis Relatively large doses of aspirin (e.g., 600 mg every 4–6 h) or nonsteroidal anti-inflammatory drugs (NSAIDs)

are sufficient to control symptoms in many cases. Generally, gastroprotective medi cations, such as proton pump inhibitors, are also prescribed. If this treatment is inadequate, or if the patient has marked local or systemic symptoms, glucocorticoids should be given. The usual starting dose is 15–40 mg of prednisone, depending on sever ity. The dose is gradually tapered over 6–8 weeks, in response to improvement in symptoms and the ESR. If a relapse occurs during glucocorticoid withdrawal, the dosage should be increased and then withdrawn more gradually. Thyroid function should be moni tored every 2–4 weeks using TSH and free T4 levels. Symptoms of thyrotoxicosis improve spontaneously but may be ameliorated by β-adrenergic blockers; antithyroid drugs play no role in treatment of the thyrotoxic phase. LT4 replacement may be needed if the hypothyroid phase is prolonged, but doses should be low enough (50–100 μg daily) to allow TSH-mediated recovery. ■ ■SILENT THYROIDITIS Painless thyroiditis, or “silent” thyroiditis, occurs in patients with under lying autoimmune thyroid disease and has a clinical course similar to that of subacute thyroiditis. The condition occurs in up to 5% of women 3–6 months after pregnancy and is then termed postpartum thyroiditis. Typically, patients have a brief phase of thyrotoxicosis last ing 2–4 weeks, followed by hypothyroidism for 4–12 weeks, and then resolution; often, however, only one phase is apparent. The condition is associated with the presence of TPO antibodies antepartum, and it is

three times more common in women with type 1 diabetes mellitus. As in subacute thyroiditis, the uptake of 99mTc pertechnetate or radioactive iodine is initially suppressed. In addition to the painless goiter, silent thyroiditis can be distinguished from subacute thyroiditis by a normal ESR and the presence of TPO antibodies. Glucocorticoid treatment is not indicated for silent thyroiditis. Severe thyrotoxic symptoms can be managed with a brief course of propranolol, 20–40 mg three or four times daily. Thyroxine replacement may be needed for the hypothyroid phase but should be withdrawn after 6–9 months, as recovery is the rule. Annual follow-up thereafter is recommended because a propor tion of these individuals develop permanent hypothyroidism. The condition may recur in subsequent pregnancies. ■ ■DRUG-INDUCED THYROIDITIS Patients receiving cytokines, such as IFN-α, tyrosine kinase inhibitors, such as sorafenib, and immune checkpoint inhibitors may develop painless thyroiditis. IFN-α, which is used to treat chronic hepatitis B or C and hematologic and skin malignancies, causes thyroid dysfunction in up to 5% of treated patients. It has been associated with painless thyroiditis, hypothyroidism, and Graves’ disease and is most common in women with TPO antibodies prior to treatment. Thyroiditis occurs in 5–20% of cancer patients treated with the immune checkpoint inhibitors pembrolizumab or nivolumab. In all cases, treatment is the same as silent thyroiditis. Routine monitoring of thyroid function tests is recommended by the American Society of Clinical Oncology. For discussion of amiodarone, see “Amiodarone Effects on Thyroid Func tion,” below. ■ ■CHRONIC THYROIDITIS Focal thyroiditis is present in 20–40% of euthyroid autopsy cases and is associated with serologic evidence of autoimmunity, particularly the presence of TPO antibodies. The most common clinically apparent cause of chronic thyroiditis is Hashimoto’s thyroiditis, an autoimmune disorder that often presents as a firm or hard goiter of variable size (Chap. 395). Riedel’s thyroiditis is a rare disorder that typically occurs in middle-aged women. It presents with an insidious, painless goiter with local symptoms due to compression of the esophagus, trachea, neck veins, or recurrent laryngeal nerves. Dense fibrosis disrupts normal gland architecture and can extend outside the thyroid cap sule. Despite these extensive histologic changes, thyroid dysfunction is uncommon. The goiter is hard, nontender, often asymmetric, and fixed, leading to suspicion of a malignancy. Diagnosis requires open biopsy as FNA biopsy is usually inadequate. Treatment is with gluco corticoids, other immunomodulatory treatments, tamoxifen, or

surgi cal relief of compressive symptoms. There is an association between Riedel's thyroiditis and IgG4-related disease causing idiopathic fibrosis at other sites (retroperitoneum, mediastinum, biliary tree, lung, and orbit) (Chap. 380). SICK EUTHYROID SYNDROME (NONTHYROIDAL ILLNESS) Any acute, severe illness can cause abnormalities of circulating TSH or thyroid hormone levels in the absence of underlying thyroid disease, making these measurements potentially misleading. The major cause of these hormonal changes is the release of cytokines such as IL-6. Unless a thyroid disorder is strongly suspected, the routine testing of thyroid function should be avoided in acutely ill patients. The most common hormone pattern in sick euthyroid syndrome (SES), also called nonthyroidal illness (NTI), is a decrease in total and unbound T3 levels (low T3 syndrome) with normal levels of T4 and TSH. The magnitude of the fall in T3 correlates with the severity of the illness. T4 conversion to T3 via peripheral 5′ (outer ring) deiodination is impaired, leading to increased reverse T3 (rT3). Since rT3 is metabolized by 5′ deiodination, its clearance is also reduced. Thus, decreased clear ance rather than increased production is the major basis for increased rT3. Also, T4 is alternately metabolized to the hormonally inactive T3 sulfate. It is generally assumed that this low T3 state is adaptive, because it can be induced in normal individuals by fasting. Teleologically, the fall in T3 may limit catabolism in starved or ill patients.

Very sick patients may exhibit a dramatic fall in total T4 and T3 levels (low T4 syndrome). With decreased tissue perfusion, muscle and liver expression of the type 3 deiodinase leads to accelerated T4 and T3 metabolism. This state has a poor prognosis. Another key factor in the fall in T4 levels is altered binding to thyroxine-binding globulin (TBG). The commonly used free T4 assays are subject to artifact when serum binding proteins are low and underestimate the true free T4 level. Fluctuation in TSH levels also creates challenges in the interpretation of thyroid function in sick patients. TSH levels may range from 0.01 to 0.1 mIU/L in very ill patients, especially with dopamine or glucocor ticoid therapy, to >20 mIU/L during the recovery phase of SES. The exact mechanisms underlying the subnormal TSH seen in 10% of sick patients and the increased TSH seen in 5% remain unclear but may be mediated by cytokines including IL-12 and IL-18. However, if the serum TSH is undetectable (<0.01 mIU/L), primary thyroid disease is more likely and endocrine evaluation should be done.

Hyperthyroidism and Other Causes of Thyrotoxicosis
CHAPTER 396 Any severe illness can induce changes in thyroid hormone levels, but certain disorders exhibit a distinctive pattern of abnormalities. Acute liver disease is associated with an initial rise in total (but not unbound) T3 and T4 levels due to TBG release; these levels become subnormal with progression to liver failure. A transient increase in total and unbound T4 levels, usually with a normal T3 level, is seen in 5–30% of acutely ill psychiatric patients. TSH values may be transiently low, normal, or high in these patients. In the early stage of HIV infection, T3 and T4 levels rise, even if there is weight loss. T3 levels fall with progres sion to AIDS, but TSH usually remains normal. Renal disease is often accompanied by low T3 concentrations, but with normal rather than increased rT3 levels, due to an unknown factor that increases uptake of rT3 into the liver. The diagnosis of NTI is challenging. Historic information may be limited, and patients often have multiple metabolic derangements. Use ful features to consider include previous history of thyroid disease and thyroid function tests, evaluation of the severity and time course of the patient's acute illness, documentation of medications that may affect thyroid function or thyroid hormone levels, and measurements of rT3 together with unbound thyroid hormones and TSH. The diagnosis of NTI is frequently presumptive, given the clinical context and pattern of laboratory

values; only resolution of the test results with clinical recovery can clearly establish this disorder. Treatment of NTI with thyroid hormone (T4 and/or T3) is controversial, but most authorities recommend monitoring the patient’s thyroid function tests during recovery, without administering thyroid hormone, unless there is historic or clinical evidence suggestive of hypothyroidism. Sufficiently large randomized controlled trials using thyroid hormone are unlikely to resolve this therapeutic controversy in the near future, because clini cal presentations and outcomes are highly variable. AMIODARONE EFFECTS ON THYROID FUNCTION Amiodarone is a commonly used type III antiarrhythmic agent (Chap. 259). It is structurally related to thyroid hormone and contains 39% iodine by weight. Thus, typical doses of amiodarone (200 mg/d) are associated with very high iodine intake, leading to greater than 40-fold increases in plasma and urinary iodine levels. Moreover, because amiodarone is stored in adipose tissue, high iodine levels persist for

> 6 months after discontinuation of the drug. Amiodarone inhibits deiodinase activity, and its metabolites function as weak antagonists of thyroid hormone action. Amiodarone has the following effects on thy roid function: (1) acute, transient suppression of thyroid function; (2) inhibition of T4 to T3 conversion causing either euthyroid hyperthyrox inemia or increased dosage requirement in LT4-treated hypothyroid patients; (3) hypothyroidism in patients susceptible to the inhibitory effects of a high iodine load; and (4) thyrotoxicosis that may be caused by either a Jod-Basedow effect from the iodine load, in the setting of MNG or incipient Graves’ disease, or a thyroiditis-like condition due to a toxic effect on thyroid follicular cells. The initiation of amiodarone treatment is associated with a transient decrease of T4 levels, reflecting the inhibitory effect of iodine on T4 release. Soon thereafter, most individuals escape from iodide-dependent

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