CHAPTER 78

Thyroid Disorders

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KEY CONCEPTS

1. The molecular biology of the thyroid hormones and their receptors has provided an in-depth understanding of the various mutations that give rise to hyper- and hypothyroidism.
2. Thyrotoxicosis is most commonly caused by Graves' disease, which is an autoimmune disorder in which thyroid-stimulating antibody (TSAb) directed against the thyrotropin receptor elicits the same biologic response as thyroid-stimulating hormone (TSH).
3. Hyperthyroidism can be treated with antithyroid drugs such as propylthiouracil (PTU) or methimazole (MMI), radioactive iodine (RAI; e.g., iodine-131 [^{131}I]), or surgical removal of the thyroid gland; selection of the initial treatment approach is based on patient characteristics such as age, concurrent physiology (e.g., pregnancy), comorbidities (e.g., chronic obstructive lung disease), and convenience.
4. PTU and MMI reduce the synthesis of thyroid hormones and are similar in efficacy and adverse effects, but their dosing ranges differ by 10-fold.
5. Response to PTU and MMI is seen in 4 to 6 weeks with a maximal response in 4 to 6 months; treatment usually continues for 1 to 2 years, and therapy is monitored by clinical signs and symptoms and by measuring the serum concentrations of TSH and free thyroxine (T_4).
6. Many patients choose to have ablative therapy with ^{131}I rather than undergo repeated courses of PTU or MMI; most receiving RAI eventually become hypothyroid and require thyroid hormone supplementation.
7. Adjunctive therapy with β-blockers controls the adrenergic symptoms of thyrotoxicosis but does not correct the underlying disorder; iodine can also be used adjunctively in preparation for surgery and acutely for thyroid storm.
8. Hypothyroidism is most often caused by an autoimmune disorder known as Hashimoto's thyroiditis, and the drug of choice for replacement therapy is levothyroxine.
9. Monitoring of levothyroxine replacement therapy is done by clinical signs and symptoms and by measuring the TSH (elevated for under-replacement, suppressed for overreplacement).

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Thyroid hormones affect the function of virtually every organ system. In the child, thyroid hormone is critical for normal growth and development. In the adult, the major role of thyroid hormone is to maintain metabolic stability. Substantial reservoirs of thyroid hormone in the thyroid gland and blood provide constant thyroid hormone availability. In addition, the hypothalamic-pituitary-thyroid axis is exquisitely sensitive to small changes in circulating thyroid hormone concentrations, and alterations in thyroid hormone secretion maintain peripheral free thyroid hormone levels within a narrow range. Patients seek medical attention for evaluation of symptoms because of abnormal thyroid hormone levels or because of diffuse or nodular thyroid enlargement.

THYROID HORMONE PHYSIOLOGY

THYROID HORMONE SYNTHESIS

The thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) are formed on thyroglobulin, a large glycoprotein synthesized within the thyroid cell (Fig. 78–1). Because of the unique tertiary structure of this glycoprotein, iodinated tyrosine residues present in thyroglobulin are able to bind together to form active thyroid hormones.[1]

Iodide is actively transported through the basolateral membrane via a sodium/iodine (Na^+/I^-) symporter from the extracellular space into the thyroid follicular cell against an electrochemical gradient, driven by the coupled transport of sodium.[2] Structurally related anions such as thiocyanate (SCN^-), perchlorate (ClO_4^-), and pertechnetate (TcO_4^-) are competitive inhibitors of iodine transport.[3] In addition, bromine, fluorine, and lithium block iodide transport into the thyroid (Table 78–1). Inorganic iodide that enters the thyroid follicular cell is ushered through the cell to the apical membrane, where it is transported into the follicular lumen by at least two efflux channels.[4,5] Located on the luminal side of the apical membrane, thyroid peroxidase oxidizes iodide and covalently binds the organified iodide to tyrosine residues of thyroglobulin (Fig. 78–2). It is interesting that although salivary glands and the gastric mucosa are able to actively transport iodide, they are unable to effectively incorporate iodide into proteins given the lack of similar oxidizing machinery. Similarly, when tyrosine molecules are iodinated on proteins other than thyroglobulin, they lack the proper tertiary structure needed to allow the formation of active thyroid hormones.

The iodinated tyrosine residues monoiodotyrosine (MIT) and diiodotyrosine (DIT) combine to form iodothyronines (Fig. 78–3). Thus, two molecules of DIT combine to form T_4, whereas MIT and DIT constitute T_3. In addition to its role in iodine organification, the hemoprotein thyroid peroxidase also catalyzes the formation of iodothyronines (coupling).

Iodine deficiency causes an increase in the ratio of MIT to DIT in thyroglobulin and leads to a relative increase in the production of T_3.[6] Because T_3 is more potent than T_4, the increase in T_3 production in

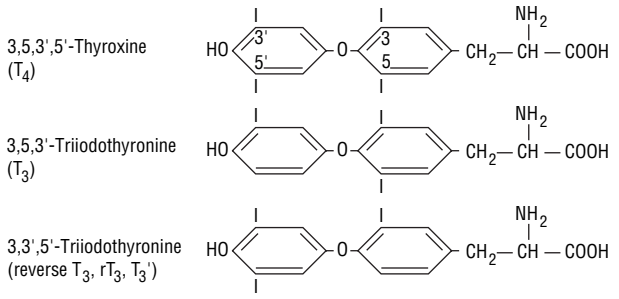

FIGURE 78-1. Structure of thyroid hormones.

iodine-depleted areas can be beneficial. The thionamide drugs used to treat hyperthyroidism inhibit thyroid peroxidase and thus block thyroid hormone synthesis.

Thyroglobulin is stored in the follicular lumen and must reenter the cell, where the process of proteolysis liberates thyroid hormone into the bloodstream. Thyroid follicles active in hormone synthesis are identified histologically by columnar epithelial cells lining follicular lumens, which are depleted of colloid. Inactive follicles are lined by cuboidal epithelial cells and are replete with colloid. Both iodide and lithium block the release of preformed thyroid hormone through poorly understood mechanisms.

T_4 and T_3 are transported in the bloodstream primarily by three proteins: thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin.[7] It is estimated that 99.96% of circulating T_4 and 99.5% of T_3 are bound to these proteins. However, only the unbound (free) thyroid hormone is able to diffuse into the cell, elicit a biologic effect, and regulate thyroid-stimulating hormone (TSH; also known as thyrotropin) secretion from the pituitary. Multiple functions have been ascribed to these transport proteins, including (1) assuring minimal urinary loss of iodide, (2) providing a mechanism for uniform tissue distribution of free hormone, and (3) transport of hormone into the central nervous system.

Whereas T_4 is secreted solely from the thyroid gland, less than 20% of T_3 is produced in the thyroid. The majority of T_3 is formed from the breakdown of T_4 catalyzed by the enzyme 5-monodeiodinase found in extrathyroidal peripheral tissues. Because the binding affinity of nuclear thyroid hormone receptors is 10 to 15 times higher for T_3 than T_4, the deiodinase enzymes play a pivotal role in determining overall metabolic activity. Three different monodeiodinase enzymes are present in the body.[8] Of the enzymes that catalyze 5'-monodeiodination, type I enzymes are present in peripheral tissues, whereas type II enzymes are found in the central nervous system, pituitary, and thyroid. Type III enzymes, found in the placenta, skin, and developing brain, inactivate T_4 and T_3 by deiodinating the inner ring at the 5'-position. The principal characteristics of these enzymes are listed in Table 78–2. T_4 may also be acted on by the enzyme 5'-monodeiodinase to form reverse T_3, but this accounts for a small component of hormone metabolism. Reverse T_3 has no known significant biologic activity. T_3 is removed from the body by deiodinative degradation

TABLE 78-1 Thyroid Hormone Synthesis and Secretion Inhibitors

Mechanism of Action	Substance
Blocks iodide transport into the thyroid	Bromine
	Fluorine
	Lithium
Impairs organification and coupling of thyroid hormones	Thionamides
	Sulfonylureas
	Sulfonamide (?)
	Salicylamide (?)
	Antipyrine (?)
Inhibits thyroid hormone secretion	Lithium iodide (large doses)

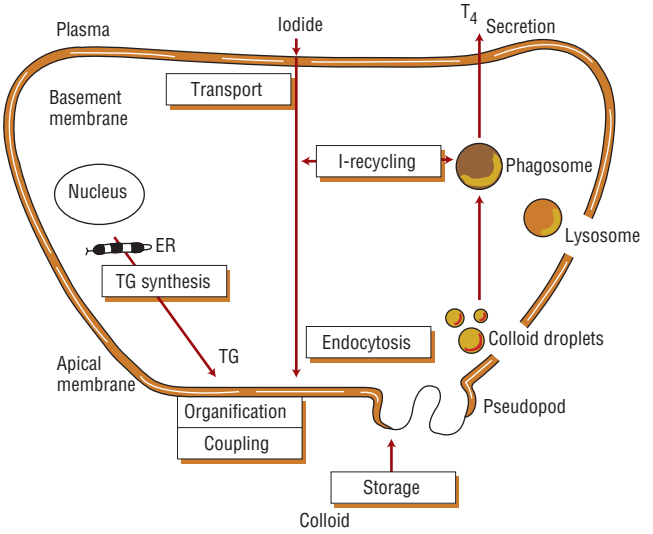

FIGURE 78-2. Thyroid hormone synthesis. Iodide is transported from the plasma, through the cell, to the apical membrane where it is organified and coupled to the thyroglobulin (TG) synthesized within the thyroid cell. Hormone stored as colloid reenters the cell through endocytosis and moves back toward the basal membrane, where T_4 is secreted. (T_4, thyroxine.)

and through the action of sulfotransferase enzyme systems to T_3 sulfate and 3,3-diiodothyronine sulfates, thus facilitating enterohepatic clearance.

The growth and function of the thyroid are stimulated by activation of the thyrotropin receptor by TSH.[9] The receptor belongs to the family of G-protein–coupled receptors. The thyrotropin receptor is coupled to the α subunit of the stimulatory guanine-nucleotide–binding protein ($G_s\alpha$), activating adenylate cyclase and increasing the accumulation of cyclic adenosine monophosphate. Through this mechanism, TSH stimulates the expression of thyroglobulin and thyroid peroxidase genes as well as increases apical iodide efflux. Somatic activating mutations in the receptor are commonly seen in autonomously functioning thyroid nodules.[10] Rarely, germline activating mutations of the TSH receptor have been reported in kindreds with Leclère's syndrome, and thyrotoxicosis can also result from germline-activating mutations in G protein signaling in McCune-

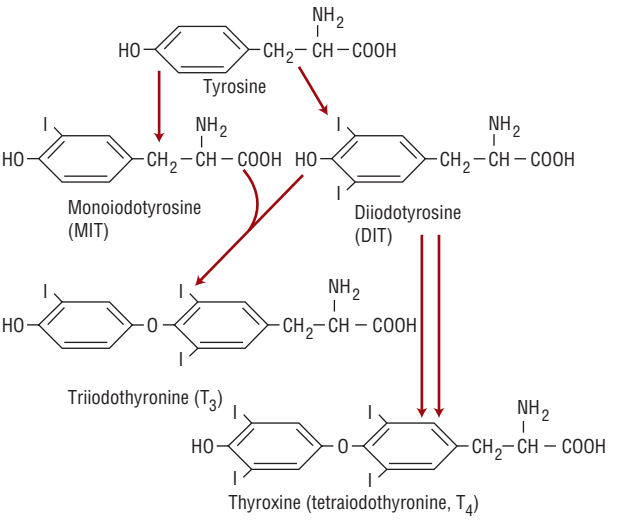

FIGURE 78-3. Scheme of coupling reactions. After tyrosine is iodinated to form monoiodotyrosine (MIT) or diiodotyrosine (DIT) (organification of the iodine), MIT and DIT combine to form triiodothyronine (T_3), or two molecules of DIT form thyroxine (T_4).

TABLE 78-2 Properties of Iodothyronine 5′-Deiodinase Isoforms

Property	Type I	Type II	Type III
Effect of propylthiouracil	Increase	Decrease	Increase
Tissue localization	Thyroid, liver, kidney	Pituitary, thyroid, CNS, brown adipose tissue	Placenta, developing brain, skin
Preferred substrate	$rT_3 > T_4 > T_3$	$T_4 > T_3$	T_3 (sulfate) > T_4
Physiologic role	Extracellular T_3 production for peripheral tissue	Intracellular T_3 production, especially for brain in hypothyroidism or iodine deficiency	Inactivation of T_4 and T_3
Developmental expression	Expressed latest in development; predominant deiodinase in adult	Expressed second; especially high in brain and brown adipose tissue	Expressed first; high in developing brain; may be important for fetal thyroid hormone metabolism

rT_3, reverse T_3; T_3, triiodothyronine; T_4, thyroxine.

Albright's syndrome.[9,11–13] Conversely, thyrotropin resistance would result from point mutations that prevent TSH binding, leading to abnormalities in the thyrotropin receptor–adenylate cyclase system and congenital hypothyroidism.[14,15] Individuals with this abnormality have high levels of TSH, but decreased thyroglobulin levels and a normal or small gland.

Thyroid hormone receptors regulate the transcription of target genes in the presence of physiologic concentrations of T_3.[16] Unlike most other nuclear receptors, thyroid hormone receptors also actively regulate gene expression in the absence of hormone, typically resulting in an opposite effect. Thyroid receptors translocate from the cytoplasm to the nucleus, interact in the nucleus with T_3, and target genes and other proteins required for basal and T_3-dependent gene transcription. Thyroid receptors exist in three isoforms, TRβ_2, TRβ_1, and TRα_1, with variation in the expression of each in differing tissues.

The production of thyroid hormone is regulated in two main ways. First, thyroid hormone is regulated by TSH secreted by the anterior pituitary. The secretion of TSH is itself under negative feedback control by the circulating level of free thyroid hormone and the positive influence of hypothalamic thyrotropin-releasing hormone (TRH). Second, extrathyroidal deiodination of T_4 to T_3 is regulated by a variety of factors including nutrition, nonthyroidal hormones, drugs, and illness.

THYROTOXICOSIS

Thyrotoxicosis results when tissues are exposed to excessive levels of T_4, T_3, or both.[17] In the National Health and Nutrition Examination Survey III (NHANES III), 0.7% of those surveyed who were not taking thyroid medications and had no history of thyroid disease had subclinical hyperthyroidism (TSH <0.1 mIU/L; and T_4 normal), and 0.5% had "clinically significant" hyperthyroidism (TSH <0.1 mIU/L; and T_4 >13.2 mcg/dL).[18] The prevalence of suppressed TSH peaked in people aged 20 to 39 years, declined in those 40 to 79 years of age, and increased again in those 80 years of age or older. Abnormal TSH levels were more common among women than among men.

CLINICAL PRESENTATION OF THYROTOXICOSIS

General

- Patients can have symptoms for an extended time period before the diagnosis of hyperthyroidism is made.

Symptoms

- The typical clinical manifestations of thyrotoxicosis include nervousness, anxiety, palpitations, emotional lability, easy fatigability, menstrual disturbances, and heat intolerance. A cardinal symptom is loss of weight concurrent with an increased appetite.

Signs

- A variety of physical signs can be elicited including warm, smooth, moist skin, exophthalmos (in Graves' disease only), pretibial myxedema (in Graves' disease only), and unusually fine hair. Separation of the end of the fingernails from the nail beds (onycholysis) may be noted. Ocular signs that result from thyrotoxicosis include retraction of the eyelids and lagging of the upper lid behind the globe when the patient looks downward (lid lag). Physical signs of a hyperdynamic circulatory state are common and include tachycardia at rest, a widened pulse pressure, and a systolic ejection murmur. Gynecomastia is sometimes noted in men. Neuromuscular examination often reveals a fine tremor of the protruded tongue and outstretched hands. Deep tendon reflexes are generally hyperactive. Thyromegaly is usually present.

Diagnosis

- Low TSH serum concentration. Elevated free and total T_3 and T_4 serum concentrations, particularly in more severe disease.
- Elevated radioactive iodine uptake (RAIU) by the thyroid gland when hormone is being overproduced; suppressed RAIU in thyrotoxicosis caused by thyroid inflammation (thyroiditis)

Other Tests

- Thyroid stimulating antibodies (TSAb)
- Thyroglobulin
- Thyrotropin receptor antibodies
- Thyroid biopsy
- Thyroperoxidase antibodies (TPO antibodies)

In the elderly (>65 years old) patient and in the patient with very severe disease, anorexia can be present as well. Elderly patients are also more likely to develop atrial fibrillation with thyrotoxicosis than younger patients. The frequency of bowel movements can increase, but frank diarrhea is unusual. Palpitations are a prominent and distressing symptom, particularly in the patient with preexisting heart disease. Proximal muscle weakness is common and is noted on climbing stairs or in getting up from a sitting position. Women might note their menses are becoming scanty and irregular. Extremely thyrotoxic (thyrotoxic storm) patients can have tachycardia, heart failure, psychosis, hyperpyrexia, and coma.[19]

DIFFERENTIAL DIAGNOSIS

If the clinical history and examination do not provide pathognomonic clues to the etiology of the patient's thyrotoxicosis, measurement of the RAIU is critical in the evaluation (Table 78–3). The normal 24-hour RAIU ranges from 10% to 30% with some regional variation because of differences in iodine intake. An elevated RAIU indicates true hyperthyroidism, that is, the patient's thyroid gland is actively overproducing T_4, T_3, or both. Conversely, a low RAIU, in the absence of iodine excess, indicates that high levels of thyroid hormone are not a consequence of thyroid gland hyperfunction but likely caused by thyroiditis or hormone ingestion. The importance

TABLE 78-3 Differential Diagnosis of Thyrotoxicosis

Increased RAIU	Decreased RAIU
TSH-induced hyperthyroidism	Inflammatory thyroid disease
TSH-secreting tumors	Subacute thyroiditis
Selective pituitary resistance to T_4	Painless thyroid
Thyroid stimulators other than TSH[a]	Ectopic thyroid tissue
TSAb (Graves' disease)	Struma ovarii
hCG (trophoblastic diseases)	Metastatic follicular carcinoma
Thyroid autonomy	Exogenous sources of thyroid hormone
Toxic adenoma	Medication
Multinodular goiter	Food

hCG, human chorionic gonadotropin; RAIU, radioactive iodine uptake; TSAb, thyroid-stimulating antibodies; TSH, thyroid-stimulating hormone; T_3, triiodothyrine; T_4, thyroxine.
[a]The RAIU can be decreased if the patient has been recently exposed to excess iodine.

of differentiating true hyperthyroidism from other causes of thyrotoxicosis lies in the widely different prognosis and treatment of the diseases in these two categories. Therapy of thyrotoxicosis associated with thyroid hyperfunction is mainly directed at decreasing the rate of thyroid hormone synthesis, secretion, or both. Such measures are ineffective in treating thyrotoxicosis that is not the result of true hyperthyroidism, because hormone synthesis and regulated hormone secretion are already at a minimum.

CAUSES OF THYROTOXICOSIS ASSOCIATED WITH ELEVATED RAIU

TSH-Induced Hyperthyroidism

To better understand these syndromes we must first review TSH biosynthesis and secretion. TSH is synthesized in the anterior pituitary as separate α- and β-subunit precursors. The α subunits from luteinizing hormone (LH), follicle-stimulating hormone (FSH), human chorionic gonadotropin (hCG), and TSH are similar, whereas the β subunits are unique and confer immunologic and biologic specificity. Free β-subunits are devoid of receptor binding and biologic activity and require combination with an α-subunit to express their activity. Criteria for the diagnosis of TSH-induced hyperthyroidism include (1) evidence of peripheral hypermetabolism, (2) diffuse thyroid gland enlargement, (3) elevated free thyroid hormone levels, and (4) elevated or inappropriately "normal" serum immunoreactive TSH concentrations. Because the pituitary gland is extremely sensitive to even minimal elevations of free T_4, a "normal" or elevated TSH level in any thyrotoxic patient indicates the inappropriate production of TSH.

TSH-Secreting Pituitary Adenomas

TSH-secreting pituitary tumors occur sporadically and release biologically active hormone that is unresponsive to normal feedback control.[20] The mean age at diagnosis is approximately 40 years of age, with women being diagnosed more commonly than men (8:7). These tumors can cosecrete prolactin or growth hormone; therefore the patients can present with amenorrhea/galactorrhea or signs of acromegaly. Most patients present with classic symptoms and signs of thyrotoxicosis. Visual-field defects can be present because of impingement of the optic chiasm by the tumor. Tumor growth and worsening visual-field defects have been reported following treatment of thyrotoxicosis, because of loss of feedback inhibition from high thyroid hormone levels.

Diagnosis of a TSH-secreting adenoma should be made by demonstrating lack of TSH response to TRH stimulation, inappropriate TSH levels, elevated α-subunit levels, and radiologic imaging; given the lack of routine availability of TRH, the other three criteria are essential. Note that some small tumors are not identified by magnetic resonance imaging (MRI). Moreover, 10% of "normal" individuals can have pituitary tumors or other benign focal lesions noted on pituitary imaging.

Transsphenoidal pituitary surgery is the treatment of choice for TSH-secreting adenomas. Pituitary gland irradiation is often given following surgery to prevent tumor recurrence. Bromocriptine and octreotide have been used to treat tumors, especially those that cosecrete prolactin.

Pituitary Resistance to Thyroid Hormone

Pituitary resistance to thyroid hormone (PRTH) refers to selective resistance of the pituitary thyrotrophs to thyroid hormone.[21] Approximately twice as many women as men have been reported with this rare, probably familial syndrome. Multiple abnormalities have been reported in the initial 50 reported cases including schizophrenia (three patients), mental retardation (two patients), short fourth metacarpals (one patient), and Marfanoid habitus (one patient). Approximately 90% of patients studied have an appropriate increase in TSH in response to TRH; conversely, the TSH will be suppressed by T_3 administration.

Patients with PRTH require treatment to reduce their elevated thyroid hormone levels. Determining the appropriate serum T_4 level is difficult because TSH cannot be used to evaluate adequacy of therapy. Any reduction in thyroid hormone carries the risk of inducing thyrotroph hyperplasia. Ideally, agents that suppress TSH secretion could be used to treat these individuals. Glucocorticoid, dopaminergic drugs, somatostatin and its analog, and thyroid hormone analogs with reduced metabolic activity have all been tried; given the ability of retinoid X receptor ligands to inhibit TSH production, drugs such as bexarotene can have therapeutic benefit in PRTH.[22]

THYROID STIMULATORS OTHER THAN TSH

Graves' Disease

Graves' disease is an autoimmune syndrome that usually includes hyperthyroidism, diffuse thyroid enlargement, and exophthalmos, and less commonly pretibial myxedema and thyroid acropachy (Fig. 78–4).[17,23,24] Graves' disease is the most common cause of hyperthyroidism, with a prevalence estimated to be 3 per 1,000 in the U.S. population. Hyperthyroidism results from the action of TSAbs, which are directed against the thyrotropin receptor on the surface of the thyroid cell.[14,15] When these immunoglobulins bind to the receptor, they activate downstream G-protein signaling and adenylate cyclase in the same manner as TSH. Autoantibodies that react with orbital muscle and fibroblast tissue in the skin are responsible for the extrathyroidal manifestations of Graves' disease, and these autoantibodies are encoded by the same germline genes that encode for other autoantibodies for striated muscle and thyroid peroxidase.[25] Clinically, the extrathyroidal disorders might not appear at the same time that hyperthyroidism develops.

There is now compelling evidence that heredity predisposes the susceptible individual to development of clinically overt autoimmune thyroid disease in the setting of appropriate environmental and hormonal triggers. A role for gender in the emergence of Graves' disease is suggested by the fact that hyperthyroidism is approximately eight times more common in women than men. Other lines of evidence support a role for heredity. First, there is a well-recognized clustering of Graves' disease within some families. Twin studies in Graves' disease have revealed that a monozygotic twin has a 35% likelihood of ultimately developing the disease compared with a 3% likelihood for a dizygotic twin, resulting in estimation that the 79% of the predisposition to Graves' disease is genetic.[26] Second, the occurrence of other autoimmune diseases, including Hashimoto's thyroiditis, is also increased in families of patients with Graves' disease. Third, several

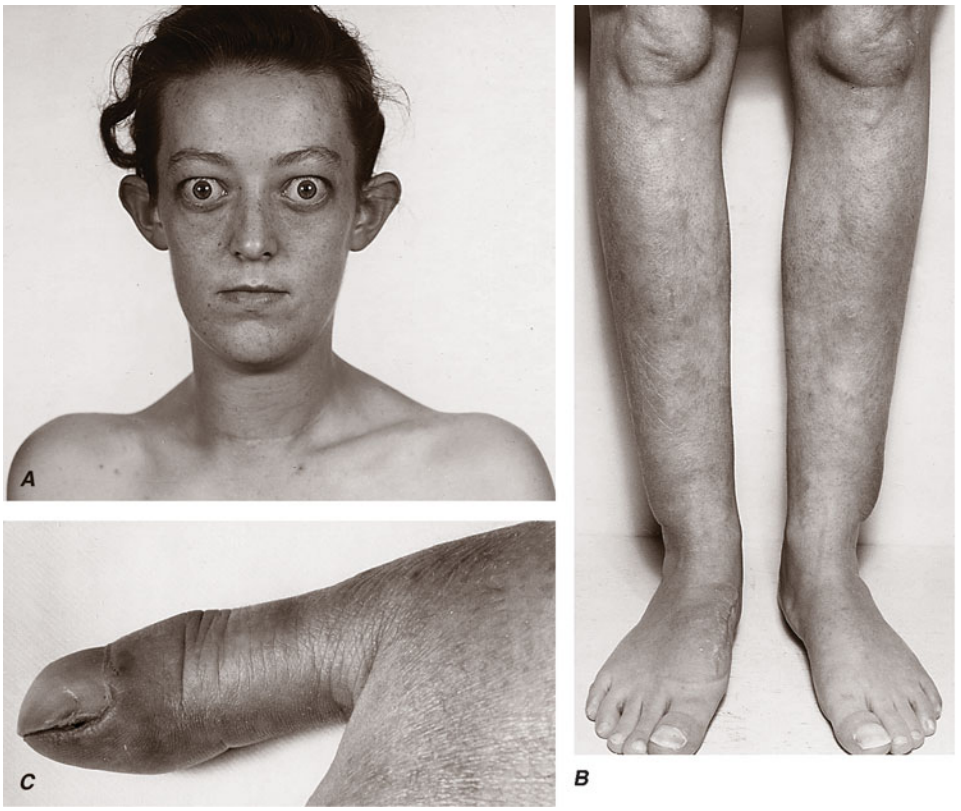

FIGURE 78-4. Features of Graves' disease. *(A)* Facial appearance in Graves' disease; lid retraction, periorbital edema, and proptosis are marked. *(B)* Thyroid dermopathy over the lateral aspects of the shins. *(C)* Thyroid acropachy. *(Reproduced with permission from Kasper DL, et al., eds. Harrison's Principles of Internal Medicine, 16th ed. New York: McGraw-Hill, 2005:2114.)*

studies have demonstrated an increased frequency of certain human leukocyte antigens (HLAs) in patients with Graves' disease. Differing HLA associations have been identified in the various ethnic groups studied. In whites, for example, the relative risk of Graves' disease in carriers of the HLA-DR3 haplotype is between 2.5 and 5, whereas lesser associations have been reported for HLA-B8 and the HLA-DQA*0501 allele.[27,28] As with other autoimmune conditions, certain polymorphisms of the T-cell immunoregulatory protein CTLA-4 have also been associated with Graves' disease. Despite these statistical associations, however, even detailed molecular genetic linkage studies have failed to identify specific genes responsible for the disease.[29]

The thyroid gland is diffusely enlarged in the majority of patients and is commonly 40 to 60 g (two to three times the normal size). The surface of the gland is either smooth or bosselated, and the consistency varies from soft to firm. In patients with severe disease, a thrill may be felt and a systolic bruit may be heard over the gland, reflecting the increased intraglandular vascularity typical of hyperplasia. Whereas the presence of any of the extrathyroidal manifestations of this syndrome, including exophthalmos, thyroid acropachy, or pretibial myxedema, in a thyrotoxic patient is pathognomonic of Graves' disease, most patients can be diagnosed on the basis of their history and examination of their diffuse goiter (see Fig. 78–4). An important clinical feature of Graves' disease is the occurrence of spontaneous remissions, albeit uncommon. The abnormalities in TSAb production can decrease or disappear over time in many patients.

The results of laboratory tests in thyrotoxic Graves' disease include an increase in the overall hormone production rate with a disproportionate increase in T_3 relative to T_4 (Table 78–4). In an occasional patient, the disproportionate overproduction of T_3 is exaggerated, with the result that only the serum T_3 concentration is increased (T_3 toxicosis). The saturation of TBG is increased because of the elevated levels of serum T_4 and T_3, which is reflected in elevated values for the T_3 resin uptake. As a result, the concentration of free T_4, free T_3, and the free T_4 and T_3 indices are increased to an even greater extent than are the measured serum total T_4 and T_3 concentrations. The TSH level will be undetectable because of negative feedback by elevated levels of thyroid hormone at the pituitary.

In the patient with manifest disease, measurement of the serum free T_4 concentration (or total T_4 and T_3 resin uptake), total T_3, and the TSH value will confirm the diagnosis of thyrotoxicosis. If the patient is not pregnant, a 24-hour RAIU should be obtained if there is any diagnostic uncertainty, for example, recent onset of symptoms or other factors suggestive of thyroiditis. An increased RAIU documents that the thyroid gland is inappropriately using the iodine to produce more thyroid hormone at a time when the patient is thyrotoxic.

Hypokalemic periodic paralysis is a rare complication of hyperthyroidism more commonly observed in Asian and Hispanic populations.[30] It presents as recurrent proximal muscle flaccidity ranging from mild weakness to total paralysis. The paralysis can be asymmetric and usually involves muscle groups that are strenuously exercised before the attack. Cognition and sensory perception are spared, whereas deep tendon reflexes are commonly markedly diminished. Hypokalemia results from a sudden shift of potassium from extracellular to intracellular sites, rather than reduced total body potassium.

TABLE 78-4 Thyroid Function Test Results in Different Thyroid Conditions

	Total T_4	Free T_4	Total T_3	T_3 Resin Uptake	Free Thyroxine Index	TSH
Normal	4.5–10.9 mcg/dL	0.8–2.7 ng/dL	60–181 ng/dL	22% to 34%	1.0–4.3 units	0.5–4.7 mIU/L
Hyperthyroid	↑↑	↑↑	↑↑↑	↑	↑↑↑	↓↓
Hypothyroid	↓↓	↓↓	↓	↓↓	↓↓↓	↑↑
Increased TBG	↑	Normal	↑	↓	Normal	Normal

TBG, thyroid-binding globulin; TSH, thyroid-stimulating hormone; T_3, triiodothyrine; T_4, thyroxine.

High carbohydrate loads and exercise provoke the attacks. Treatment includes correcting the hyperthyroid state, potassium administration, spironolactone to conserve potassium, and propranolol to minimize intracellular shifts.

Trophoblastic Diseases

Human chorionic gonadotropin (hCG) is a stimulator of the TSH receptor and can cause hyperthyroidism.[31] The basis for the thyrotropic effect of hCG is the structural similarity of hCG to TSH (similar α-subunits and unique β subunits). In hyperthyroid patients with very high hCG levels, serum TSH can be inappropriately detectable because of the weak cross-reactivity of hCG in the radioimmunoassay for TSH. In patients with hyperthyroidism caused by trophoblastic tumors, serum hCG levels usually exceed 300 units/mL and always exceed 100 units/mL. The mean peak hCG level in normal pregnancy is 50 units/mL. On a molar basis, hCG has only 1/10,000 the activity of pituitary TSH in mouse bioassays. Nevertheless, this thyrotropic activity can be very substantial in patients with trophoblastic tumors, whose serum hCG concentrations can reach 2,000 units/mL.

THYROID AUTONOMY

Toxic Adenoma

An autonomous thyroid nodule is a discrete thyroid mass whose function is independent of pituitary and TSH control.[32] The prevalence of toxic adenoma ranges from about 2% to 9% of thyrotoxic patients, and depends on iodine availability and geographic location. Toxic adenomas arise from gain-of-function somatic mutations of the TSH receptor, or less commonly the $G_s\alpha$ protein; more than a dozen TSH receptor mutations have been described.[10] These nodules can be referred to as a toxic adenoma or a "hot" nodule because of their persistent uptake on a radioiodine thyroid scan, despite suppressed uptake in the surrounding non-nodular gland (Fig. 78–5). The amount of thyroid hormone produced by an autonomous nodule is mass related. Therefore hyperthyroidism usually occurs with larger nodules (i.e., those >3 cm in diameter). Older patients (>60 years of age) are more likely (up to 60%) to be thyrotoxic from autonomous nodules than are younger (<60 years of age) patients (12%). There are many reports of isolated elevation of serum T_3 in patients with autonomously functioning nodules. Therefore if the T_4 level is normal, a T_3 level must be measured to rule out T_3 toxicosis.

If autonomous function is suspected, but the TSH is normal, the diagnosis can be confirmed by a failure of the autonomous nodule to decrease its iodine uptake during exogenous T_3 administration sufficient to suppress TSH. Surgical resection, thionamides, percutaneous ethanol injection, and RAI ablation are treatment options, but as thionamides do not halt the proliferative process in the nodule, definitive therapies are recommended.[33] Ethanol ablation can be associated with pain and damage to surrounding extrathyroidal tissues, limiting its acceptance in the United States. It has been hypothesized that sublethal radiation doses received by the surrounding non-nodular thyroid tissue during RAI therapy of toxic nodules can lead to induction of thyroid cancer, and excess thyroid cancer mortality has recently been associated with RAI therapy of toxic nodular disease. Thus, an autonomously functioning nodule, if not large enough to cause thyrotoxicosis, can often be observed conservatively without therapy.

Multinodular Goiters

In multinodular goiters (MNGs; Plummer's disease), follicles with autonomous function coexist with normal or even nonfunctioning follicles.[32] The pathogenesis of MNG is thought to be similar to that of toxic adenoma: diffuse hyperplasia caused by goitrogenic stimuli, leading to mutations and clonal expansion of benign neoplasms.[34] The functional status of the nodule(s) depends on the nature of the underlying mutations, whether activating such as TSH-receptor mutations or inhibitory such as ras mutations. Thyrotoxicosis in a MNG occurs when a sufficient mass of autonomous follicles generates enough thyroid hormone to exceed the needs of the patient. It is not surprising that this type of hyperthyroidism develops insidiously over a period of several years and predominantly affects older individuals with long-standing goiters. The patient's complaints of weight loss, depression, anxiety, and insomnia might be attributed to old age. Any unexplained chronic illness in an elderly patient presenting with a MNG calls for the exclusion of hidden thyrotoxicosis.[35] Third-generation TSH assays and T_3 suppression testing can be useful in detecting subclinical hyperthyroidism.[36]

A thyroid scan will show patchy areas of autonomously functioning thyroid tissue intermixed with hypofunctioning areas. When the patient is euthyroid, therapy is based on the need to reduce goiter size because of mass-related symptoms such as dysphagia. Doses of thyroid hormone sufficient to suppress TSH levels can slow goiter growth or cause some degree of shrinkage, but in general suppression

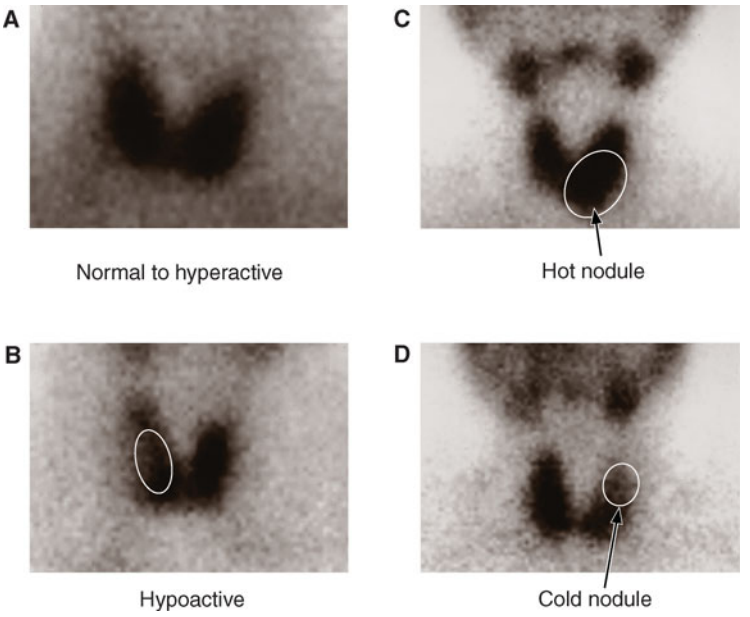

FIGURE 78-5. Radioiodine thyroid scans. *(A)* Normal to increased thyroid uptake of iodine-125 (^{125}I). *(B)* Thyroid with marked decrease in ^{125}I uptake in a large palpable mass. *(C)* Increased ^{125}I uptake isolated to a single nodule, the "hot nodule." *(D)* Decreased thyroid ^{125}I uptake in an isolated region, the "cold nodule." *(Reproduced with permission from Molina PE. Endocrine Physiology, 2nd ed. New York: McGraw-Hill, 2006:90. Images courtesy of Dr. Luis Linares, Memorial Medical Center, New Orleans, LA.)*

therapy for nodular disease is inadequate to address mass effect.[37] The preferred treatment for toxic MNG is RAI or surgery. Surgery is usually selected for younger (<60 years old) patients and patients in whom large goiters impinge on vital organs. Alternatively, percutaneous injection of 95% ethanol has also been used to destroy single or multinodular adenomas with a 5-year success rate approaching 80%.

CAUSES OF THYROTOXICOSIS ASSOCIATED WITH SUPPRESSED RAIU

Inflammatory Thyroid Disease

Subacute Thyroiditis Painful subacute (granulomatous or de Quervain's) thyroiditis often develops after a viral syndrome but rarely has a specific virus been identified in thyroid parenchyma.[38] A genetic predisposition exists with markedly higher risk for developing subacute thyroiditis in patients with HLA-Bw35. Systemic symptoms often accompany the syndrome, including fever, malaise, and myalgia, in addition to those symptoms caused by thyrotoxicosis. Typically, patients complain of severe pain in the thyroid region, which often extends to the ear on the affected side.[39] With time, the pain can migrate from one side of the gland to the other. On physical examination, the thyroid gland is firm and exquisitely tender. Signs of thyrotoxicosis are present.

Thyroid function tests typically run a triphasic course. Initially, serum T_4 levels are elevated because of release of preformed thyroid hormone from disrupted follicles. The 24-hour RAIU during this time is less than 2% because of thyroid inflammation and TSH suppression by the elevated T_4 level. As the disease progresses, intrathyroidal hormone stores are depleted, and the patient can become mildly hypothyroid with an appropriately elevated TSH level. During the recovery phase thyroid hormone stores are replenished, and serum TSH elevation gradually returns to normal. Recovery is generally complete within 2 to 6 months. Most patients remain euthyroid, and recurrences of painful thyroiditis are extremely rare. The patient with painful thyroiditis should be reassured that the disease is self-limited and is unlikely to recur. Thyrotoxic symptoms can be relieved with β-blockers. Aspirin (650 mg orally every 6 hours) will usually relieve the pain. Occasionally, prednisone (20 mg orally three times a day) must be used to suppress the inflammatory process. Antithyroid drugs are not indicated because they do not decrease the release of preformed thyroid hormone.

Painless Thyroiditis Since its description in 1975, painless (silent, lymphocytic) thyroiditis has been recognized as a common cause of thyrotoxicosis and can represent up to 15% of cases of thyrotoxicosis in North America.[40] In the setting of development of lymphocytic thyroiditis during the first 12 months after the end of pregnancy, the condition is also called "postpartum thyroiditis."[41] The etiology is not fully understood and may be heterogeneous, but evidence indicates that autoimmunity underlies most cases. There is an increased frequency of HLA-DR3 and DR5 in patients with subacute thyroiditis; nonendocrine autoimmune diseases are also more common. Histologically, diffuse lymphocytic infiltration is generally identified. The triphasic course of this illness mimics that of subacute thyroiditis. Most patients present with mild thyrotoxic symptoms. Lid retraction and lid lag are present, but exophthalmos is absent. The thyroid gland can be diffusely enlarged, but thyroid tenderness is absent.

The 24-hour RAIU will typically be suppressed to less than 2% during the thyrotoxic phase of painless thyroiditis. Antithyroglobulin and antimicrosomal antibody levels are elevated in more than 50% of patients. Patients with mild hyperthyroidism and painless thyroiditis should be reassured that they have a self-limited disease, although patients with postpartum thyroiditis can experience recurrence of the disease with subsequent pregnancies. As with other thyrotoxic syndromes, adrenergic symptoms can be ameliorated with propranolol or metoprolol. Antithyroid drugs, which inhibit new hormone synthesis, are not indicated because they do not decrease the release of preformed thyroid hormone.

Ectopic Thyroid Tissue

Struma Ovarii Struma ovarii is a teratoma of the ovary that contains differentiated thyroid follicular cells and is capable of making thyroid hormone.[42] This extremely rare cause of thyrotoxicosis is suggested by the absence of thyroid enlargement in a thyrotoxic patient with a suppressed RAIU in the neck and no findings to suggest thyroiditis. The diagnosis is established by localizing functioning thyroid tissue in the ovary with whole-body radioactive iodine (^{131}I) scanning. Interestingly, struma ovarii without associated hyperthyroidism is much more common than struma ovarii associated with hyperthyroidism. Because the tissue is neoplastic and potentially malignant, combined surgical and radioiodine treatment of malignant struma ovarii for both monitoring and therapy of relapse is the recommended treatment.

Follicular Cancer In widely metastatic differentiated papillary or follicular carcinomas with relatively well-preserved function, sufficient thyroid hormone can be synthesized and secreted to produce thyrotoxicosis.[43,44] In most instances, a previous diagnosis of thyroid malignancy has been made. The diagnosis can be confirmed by whole-body ^{131}I scanning. Treatment with ^{131}I is generally effective at ablating functioning thyroid metastases.

Exogenous Sources of Thyroid Hormone

Thyrotoxicosis factitia is produced by the ingestion of exogenous thyroid hormone.[45] Obesity is the most common nonthyroidal disorder for which thyroid hormone is inappropriately used, but thyroid hormone has been used for almost every conceivable problem from menstrual irregularities and infertility to hypercholesterolemia and baldness. Despite there being little evidence to suggest that these patients benefit from treatment with thyroid hormone, the physician or patient can gradually increase the dose of hormone employed in an attempt to gain the desired effect. Obviously, thyrotoxicosis factitia can also occur when too large a dose of thyroid hormone is employed for conditions in which it is likely to be beneficial, such as differentiated thyroid carcinoma. Rarely, thyrotoxicosis factitia is caused by the purposeful and secretive ingestion of thyroid hormone by disturbed patients (usually with a medical background) who wish to obtain attention or lose weight.

Thyrotoxicosis factitia should be suspected in a thyrotoxic patient without evidence of increased hormone production, thyroidal inflammation, or ectopic thyroid tissue. The RAIU uptake is at low levels because the patient's thyroid gland function is suppressed by the exogenous thyroid hormone.[46] Measurement of plasma thyroglobulin (TG) is a valuable laboratory aid in the diagnosis of thyrotoxicosis factitia. TG is normally secreted in small amounts by the thyroid gland; however, when thyroid hormone is taken orally, very low amounts of thyroglobulin are detectable in the plasma. In other entities characterized by a low RAIU, such as thyroiditis, leakage of preformed thyroid hormone results in elevated thyroglobulin levels. If a history of thyroid hormone ingestion is elicited or deduced, exogenous thyroid hormone should be withheld for between 4 and 6 weeks and thyroid function tests repeated to document that the euthyroid state has been restored. Rarely, thyroid hormone analogues or metabolites can be the drug of abuse, specific detection of which can be difficult with standard thyroid hormone assays. For example, tiratricol (3,5,3-triiodothyroacetic acid [TRIAC]), an endogenous metabolite of T_3 that has been used for weight loss and paradoxically by body builders, will suppress TSH at high enough doses and may cross-react in many T_3 immunoassays; thus, thyrotoxicosis factitia because of tiratricol abuse can be misinterpreted as T_3-toxicosis.[47]

Amiodarone can induce thyrotoxicosis (2% to 3% of patients), hypothyroidism, or euthyroid hyperthyroxinemia, depending on the underlying thyroid pathology or lack thereof.[48] Because amiodarone contains 37% iodine by weight, approximately 6 mg/day of iodine is released for each 200 mg of amiodarone, 1,000 times greater than the recommended daily amount of iodine of 200 mcg/day. As a result of this iodine overload, iodine-exacerbated thyroid dysfunction commonly occurs among those patients with preexisting thyroid disease: thyrotoxicosis in patients with hyperthyroidism or euthyroid nodular autonomy, and hypothyroidism in patients with autoimmune thyroid disease. In contrast to hyperthyroidism induced by amiodarone (type I), destructive thyroiditis with loss of thyroglobulin and thyroid hormones also occurs (type II), typically among individuals with otherwise normal glands. The two types of amiodarone-induced thyrotoxicosis can be differentiated using color flow Doppler ultrasonography. Such distinction is critically important, given the therapeutic implications of the two syndromes: type I amiodarone-induced hyperthyroidism responds somewhat to thionamides, whereas type II can require glucocorticoids or iopanoic acid.[49–51] Obviously, RAI therapy is inappropriate, in type I because of the drug-induced iodine excess and in type II because of lack of increased hormone synthesis. The manifestations of amiodarone-induced thyrotoxicosis can be atypical symptoms such as ventricular tachycardia and exacerbation of underlying chronic obstructive pulmonary disease, both of which are even more significant given the severe underlying cardiac pathology which led to the use of the drug in the first place. Amiodarone also directly interferes with type I 5'-deiodinase, leading to reduced conversion of T_4 to T_3 and hyperthyroxinemia without thyrotoxicosis.

TREATMENT

Hyperthyroidism

■ DESIRED OUTCOMES

3 Three common treatment modalities are used in the management of hyperthyroidism: surgery, antithyroid medications, and RAI (Table 78–5). The overall therapeutic objectives are to eliminate the excess thyroid hormone and minimize the symptoms and long-term consequences of hyperthyroidism. Therapy must be individualized based on the type and severity of hyperthyroidism, patient age and gender, existence of nonthyroidal conditions, and response to previous therapy.[52,53] Clinical guidelines for the treatment of hyperthyroidism have been published by various groups.[54–56]

■ NONPHARMACOLOGIC THERAPY

Surgical removal of the hypersecreting thyroid gland became feasible in 1923 when Plummer discovered that iodine reduced the gland's vascularity, making this definitive procedure possible. Surgery should be considered in patients with a large thyroid gland (>80 g), severe ophthalmopathy, and a lack of remission on antithyroid drug treatment. In case of cosmetic or pressure symptoms, the choice in MNG stands between surgery, which is still the first choice, and radioiodine if uptake is adequate (hot). In addition to surgery, the solitary nodule, whether hot or cold, can be treated with percutaneous ethanol injection therapy. If hot, radioiodine is the therapy of choice.[57] Traditional preparation of the patient for thyroidectomy includes PTU or MMI until the patient is biochemically euthyroid (usually 6 to 8 weeks), followed by the addition of iodides (500 mg/day) for 10 to 14 days before surgery to decrease the vascularity of the gland. Levothyroxine can be added to maintain the euthyroid state while the thionamides are continued. Iodine supplementation in iodine-deficient areas of the country can lead to a greater reduction in remnant volume in nontoxic goiter.[58] Propranolol for several weeks preoperatively and 7 to 10 days after surgery has also been used to maintain a pulse rate of less than 90 beats/min. Combined pretreatment with propranolol and 10 to 14 days of potassium iodide also has been advocated.

The overall morbidity rate with surgery is 2.7%. Hyperthyroidism persists or recurs in 0.6% to 17.9% of patients after thyroidectomy for Graves' disease and is more common in children. The most common complications of surgery include hypothyroidism (up to about 49%), hypoparathyroidism (up to 3.9%), and vocal cord abnormalities (up to 5.4%). The frequent occurrence of hypothyroidism following surgery requires periodic followup for identification and treatment of these patients.[59,60]

■ PHARMACOLOGIC THERAPY

Antithyroid Medications

Thiourea Drugs Two drugs within this category, PTU and MMI, are approved for the treatment of hyperthyroidism in the United States.[61] They are classified as thioureylenes (thionamides), which incorporate a N—C—S = N group into their ring structures.

Mechanism of Action. PTU and MMI share several mechanisms to inhibit the biosynthesis of thyroid hormone.[17] These drugs serve as preferential substrates for the iodinating intermediate of thyroid peroxidase and divert iodine away from potential iodination sites in thyroglobulin. This prevents subsequent incorporation of iodine into

TABLE 78-5 Treatments for Hyperthyroidism Caused by Graves' Disease

Treatment	Advantages	Disadvantages	Comment
Antithyroid drugs	Noninvasive Lower initial cost Low risk of permanent hypothyroidism Possible remissions because of immune effects	Low cure rate (30–80%; average 40–50%) Adverse drug reactions Drug compliance	First-line treatment in children, adolescents, and in pregnancy Initial treatment in severe cases or preoperative preparation
Radioactive iodine (^{131}I)	Cure of hyperthyroidism Most cost effective	Permanent hypothyroidism almost inevitable Might worsen ophthalmopathy Pregnancy must be deferred for 6–12 months; no breast-feeding Small potential risk of exacerbation of hyperthyroidism	Best treatment for toxic nodules and toxic multinodular goiter
Surgery	Rapid, effective treatment, especially in patients with large goiters	Most invasive Potential complications (recurrent laryngeal nerve damage, hypoparathyroidism) Most costly Permanent hypothyroidism Pain, scar	Potential in pregnancy if major side-effect from antithyroid Useful when coexisting suspicious nodule present Option for patients who refuse radioiodine

iodotyrosines and ultimately iodothyronine (*organification*). Second, they inhibit coupling of monoiodotyrosine and diiodotyrosine to form T_4 and T_3. The coupling reaction can be more sensitive to these drugs than the iodination reaction. Experimentally, these drugs exhibit immunosuppressive effects, although the clinical relevance of this finding is unclear. In patients with Graves' disease, antithyroid drug treatment has been associated with lower TSAb titers and restoration of normal suppressor T-cell function. However, perchlorate, which has a different mechanism of action, also decreases TSAbs, suggesting that normalization of the thyroid hormone level can itself improve the abnormal immune function. PTU inhibits the peripheral conversion of T_4 to T_3. This effect is acutely dose related and occurs within hours of PTU administration. MMI does not have this effect. Over time, depletion of stored hormone and lack of continuing synthesis of thyroid hormone results in the clinical effects of these drugs.

Pharmacokinetics. Both antithyroid drugs are well absorbed (80% to 95%) from the gastrointestinal tract, with peak serum concentrations approximately 1 hour after ingestion. The plasma half-life ranges of PTU and MMI are 1 to 2.5 hours and 6 to 9 hours, respectively, and are not appreciably affected by thyroid status. Urinary excretion is approximately 35% for PTU and less than 10% for MMI. These drugs are actively concentrated in the thyroid gland, which can account for the disparity between their relatively short plasma half-lives and the effectiveness of once-daily dosing regimens even with PTU. Approximately 60% to 80% of PTU is bound to plasma albumin, whereas MMI is not protein-bound. MMI readily crosses the placenta and appears in breast milk. Older studies suggested that PTU crosses the placental membranes only one-tenth as well as MMI; however, these studies were done in the course of therapeutic abortion early in pregnancy. Newer studies show little difference between fetal concentrations of PTU and MMI, and both are associated with elevated TSH in approximately 20% and low T_4 in approximately 7% of the fetuses.[62]

Dosing and Monitoring. PTU is available as 50-mg tablets and MMI as 5- and 10-mg tablets. MMI is approximately 10 times more potent than PTU. Initial therapy with PTU ranges from 300 to 600 mg daily, usually in three or four divided doses. MMI is given in three divided doses totaling 30 to 60 mg/day. Although the traditional recommendation is for divided doses, evidence exists that both drugs can be given as single daily doses. Patients with severe hyperthyroidism can require larger initial doses, and some might respond better at these larger doses if the dose is divided. The maximal blocking doses of PTU and MMI are 1,200 and 120 mg daily, respectively. Once the intrathyroidal pool of thyroid hormone is reduced, and new hormone synthesis is sufficiently blocked, clinical improvement should ensue. Usually within 4 to 8 weeks of initiating therapy, symptoms are diminished, and circulating thyroid hormone levels are returning to normal. At this time the tapering regimen can be started. Changes in dose for each drug should be made on a monthly basis, because the endogenously produced T_4 will reach a new steady-state concentration in this interval. Typical ranges of daily maintenance doses for PTU and MMI are 50 to 300 mg and 5 to 30 mg, respectively.

If the objective of therapy is to induce a long-term remission, the patient should remain on continuous antithyroid drug therapy for 12 to 24 months. Antithyroid drug therapy induces permanent remission rates of 10% to 98%, with an overall average of about 40% to 50%.[63] This is much higher than the remission rate seen with propranolol alone, which is reported to range from 22% to 36%. Patient characteristics for a favorable outcome include older patients (>40 years of age), low ratio of T_4 to T_3 (<20), a small goiter (<50 g), short duration of disease (<6 months), no previous history of relapse with antithyroid drugs, duration of therapy 1 to 2 years or longer, and low TSAb titers at baseline or a reduction with treatment.[17] It is important that patients be followed every 6 to 12 months after remission occurs.

6 If a relapse occurs, alternate therapy with RAI is preferred to a second course of antithyroid drugs. Relapses seem to plateau after approximately 5 years, and eventually 5% to 20% of patients will develop spontaneous hypothyroidism.

Concurrent administration of T_4 with thionamide therapy for thyrotoxicosis and subclinical hyperthyroidism can reduce autoantibodies directed toward the thyroid gland and improve the remission rate; however, these effects have not been consistently observed in all studies.[63,64] In a Japanese study, adjunctive treatment with T_4 was associated with a 20-fold reduction in the recurrence rate of Graves' disease compared with the recurrence rate seen in patients treated with antithyroid drugs alone. Attempts to reproduce these results in American and European patients with Graves' disease have failed to show any delay or reduction in the recurrence of Graves' disease with T_4 administration.[65]

Adverse Effects. Minor adverse reactions to PTU and MMI have an overall incidence of 5% to 25% depending on the dose and the drug, whereas major adverse effects occur in 1.5% to 4.6% of patients receiving these drugs.[61,66] Pruritic maculopapular rashes (sometimes associated with vasculitis based on skin biopsy), arthralgias, and fevers occur in up to 5% of patients and can occur at greater frequency with higher doses and in children. Rashes often disappear spontaneously, but if persistent, can be managed with antihistamines.

Perhaps one of the most common side effects is a benign transient leukopenia characterized by a white blood cell (WBC) count of less than 4,000/mm^3. This condition occurs in up to 12% of adults and 25% of children, and sometimes can be confused with mild leukopenia seen in Graves' disease. This mild leukopenia is not a harbinger of the more serious adverse effect of agranulocytosis, so therapy can usually be continued. If a minor adverse reaction occurs with one antithyroid drug, the alternate thiourea can be tried, but cross-sensitivity occurs in approximately 50% of patients.[61]

Agranulocytosis is the most serious adverse effect of thiourea drug therapy and is characterized by fever, malaise, gingivitis, oropharyngeal infection, and a granulocyte count less than 250/mm^3.[61] These drugs are concentrated in granulocytes, and this reaction can represent a direct toxic effect rather than hypersensitivity. This toxic reaction has occurred with both thioureas, and the incidence varies from 0.5% to 6%. It is higher in patients older than age 40 years receiving a MMI dose greater than 40 mg/day or the equivalent dose of PTU, and is linked to HLA class II genes containing the DRB1*08032 allele.[67] Agranulocytosis almost always develops in the first 3 months of therapy. Because the onset is sudden, routine monitoring is not recommended. Colony-stimulating factors have been used with some success to restore cell counts to normal, but it is unclear how effective this form of therapy is to routine supportive care.[68,69] Peripheral lymphocytes obtained from patients with PTU-induced agranulocytosis undergo transformation in the presence of other thioamides, suggesting that these severe reactions are immunologically mediated, and patients should not receive other thionamides. Aplastic anemia has been reported with MMI and can be associated with an inhibitor to colony-forming units. Once antithyroid drugs are discontinued, clinical improvement is seen over several days to weeks. Patients should be counseled to discontinue therapy and contact their physician when flu-like symptoms such as fever, malaise, or sore throat develop.

Arthralgias and a lupus-like syndrome (sometimes in the absence of antinuclear antibodies) have been reported in 4% to 5% of patients. This generally occurs after 6 months of therapy. Uncommonly, polymyositis, presenting as proximal muscle weakness and elevated creatine phosphokinase, has been reported with PTU administration. Gastrointestinal intolerance is also reported to occur in 4% to 5% of patients. Hepatotoxicity, which usually occurs within the first 3 months of therapy, can be seen with both MMI and PTU with a prevalence of approximately 1.3%.[70] In mice, MMI undergoes

epoxidation of the C-4,5 double bond by cytochrome P450 enzymes, and after being hydrolyzed, the resulting epoxide is decomposed to form *N*-methylthiourea, a proximate toxicant.[71] At moderate doses, some authors have found that initial enzyme elevations eventually normalize in most patients with continued therapy.[72] High doses of PTU are more likely to produce severe hepatitis and even death. Discontinuation of therapy usually results in complete resolution of hepatitis. Patients receiving interferon products for hepatitis C or other disorders can develop hyper- or hypothyroidism along with liver enzyme abnormalities.[73] Although older reports suggested that congenital skin defects (aplasia cutis) can be caused by MMI and carbimazole, a registry review from the Netherlands could not find an association between maternal use of these drugs and skin defects.[74] Hypoprothrombinemia is a rare complication of thionamide therapy. Patients who have experienced a major adverse reaction to one thiourea drug should not be converted to the alternate drug because of cross-sensitivity.

Iodides Iodide was the first form of drug therapy for Graves' disease. Its mechanism of action is to acutely block thyroid hormone release, inhibit thyroid hormone biosynthesis by interfering with intrathyroidal iodide use (the Wolff-Chaikoff effect), and decrease the size and vascularity of the gland. This early inhibitory effect provides symptom improvement within 2 to 7 days of initiating therapy, and serum T_4 and T_3 concentrations can be reduced for a few weeks. Despite the reduced release of T_4 and T_3, thyroid hormone synthesis continues at an accelerated rate, resulting in a gland rich in stored hormones. The normal and hyperfunctioning thyroid soon escapes from this inhibitory effect within 1 to 2 weeks by decreasing the active transfer of iodide into the gland. Iodides are often used as adjunctive therapy to prepare a patient with Graves' disease for surgery, to acutely inhibit thyroid hormone release and quickly attain the euthyroid state in severely thyrotoxic patients with cardiac decompensation, or to inhibit thyroid hormone release following radioactive iodine therapy. However, large doses of iodine can exacerbate hyperthyroidism or indeed precipitate hyperthyroidism in some previously euthyroid individuals (Jod-Basedow's disease).[75] This Jod-Basedow's phenomenon is most common in iodine-deficient areas, particularly in patients with preexisting nontoxic goiter. Iodide is contraindicated in toxic MNG.

Potassium iodide is available either as a saturated solution (saturated solution of potassium iodide [SSKI]), which contains 38 mg of iodide per drop, or as Lugol solution, which contains 6.3 mg of iodide per drop. The typical starting dose of SSKI is 3 to 10 drops daily (120 to 400 mg) in water or juice. There is no documented advantage to using doses in excess of 6 to 8 mg/day. When used to prepare a patient for surgery, it should be administered 7 to 14 days preoperatively. As an adjunct to RAI, SSKI should not be used before, but rather 3 to 7 days after RAI treatment, so that the radioactive iodide can concentrate in the thyroid. The most frequent toxic effect with iodide therapy is hypersensitivity reactions (skin rashes, drug fever, rhinitis, and conjunctivitis); salivary gland swelling; "iodism" (metallic taste, burning mouth and throat, sore teeth and gums, symptoms of a head cold, and sometimes stomach upset and diarrhea); and gynecomastia.

Other compounds containing organic iodide have also been used therapeutically for hyperthyroidism. These include various radiologic contrast media that share a triiodo- and monoaminobenzene ring with a propionic acid chain (e.g., iopanoic acid and sodium ipodate). The effect of these compounds is a result of the iodine content inhibiting thyroid hormone release as well as competitive inhibition of 5'-monodeiodinase conversion related to their structures, which resemble thyroid analogs.[76]

Adrenergic Blockers 7 Because many of the manifestations of hyperthyroidism are mediated by β-adrenergic receptors, β-blockers (especially propranolol) have been used widely to ameliorate thyrotoxic symptoms such as palpitations, anxiety, tremor, and heat intolerance. Although β-blockers are quite effective for symptom control, they have no effect on the urinary excretion of calcium, phosphorus, hydroxyproline, creatinine, or various amino acids, suggesting a lack of effect on peripheral thyrotoxicosis and protein metabolism. Furthermore, β-blockers do not reduce TSAb nor prevent thyroid storm. Propranolol and nadolol partially block the conversion of T_4 to T_3, but this contribution to the overall therapeutic effect is small in magnitude. Inhibition of conversion of T_4 to T_3 is mediated by *d*-propranolol, which is devoid of β-blocking activity, and *l*-propranolol, which is responsible for the antiadrenergic effects and has little effect on the conversion.

β-Blockers are usually used as adjunctive therapy with antithyroid drugs, RAI, or iodides when treating Graves' disease or toxic nodules; in preparation for surgery; or in thyroid storm. The only conditions for which β-blockers are primary therapy for thyrotoxicosis are thyroiditis and iodine-induced hyperthyroidism. The dose of propranolol required to relieve adrenergic symptoms is variable, but an initial dose of 20 to 40 mg four times daily is effective (heart rate <90 beats/min) for most patients. Younger or more severely toxic patients can require as much as 240 to 480 mg/day because there seems to be an increased clearance rate in these patients. β-Blockers are contraindicated in patients with decompensated heart failure unless it is caused solely by tachycardia (high output). Nonselective agents and those lacking intrinsic sympathomimetic activity should be used with caution in patients with asthma and bronchospastic chronic obstructive lung disease. β-Blockers that are cardioselective and have intrinsic sympathomimetic activity may have a slight margin of safety in these situations. Other patients in whom contraindications exist are those with sinus bradycardia, those receiving monoamine oxidase inhibitors or tricyclic antidepressants, and those with spontaneous hypoglycemia. β-Blockers can also prolong gestation and labor during pregnancy. Other side effects include nausea, vomiting, anxiety, insomnia, light-headedness, bradycardia, and hematologic disturbances.

Antiadrenergic agents such as centrally acting sympatholytics and calcium channel antagonists may have some role in the symptomatic treatment of hyperthyroidism. These drugs might be useful when contraindications to β-blockade exist. When compared to nadolol 40 mg twice daily, clonidine 150 mcg twice daily reduced plasma catecholamines, whereas nadolol increased both epinephrine and norepinephrine after 1 week of treatment. Diltiazem 120 mg given every 8 hours reduced heart rate by 17%; fewer ventricular extrasystoles were noted after 10 days of therapy, and diltiazem has been shown to be comparable to propranolol in lowering heart rate and blood pressure.

Radioactive Iodine Although other radioisotopes have been used to ablate thyroid tissue, sodium iodide 131 (^{131}I) is considered to be the agent of choice for Graves' disease, toxic autonomous nodules, and toxic MNGs.[77,78] RAI is administered as a colorless and tasteless liquid that is well absorbed and concentrates in the thyroid. Sodium iodide 131 is a β- and γ-emitter with a tissue penetration of 2 mm and a half-life of 8 days. Other organs take up ^{131}I, but the thyroid gland is the only organ in which organification of the absorbed iodine takes place. Initially, RAI disrupts hormone synthesis by incorporating into thyroid hormones and thyroglobulin. Over a period of weeks, follicles that have taken up RAI and surrounding follicles develop evidence of cellular necrosis, breakdown of follicles, development of bizarre cell forms, nuclear pyknosis, and destruction of small vessels within the gland, leading to edema and fibrosis of the interstitial tissue. Pregnancy is an absolute contraindication to the use of RAI.

β-Blockers can be given any time without compromising RAI therapy, accounting for their role as a mainstay of adjunctive therapy to RAI treatment. If iodides are administered, they should be given 3 to 7 days after RAI to prevent interference with the uptake of RAI in the thyroid gland. Because thyroid hormone levels

will transiently increase following RAI treatment because of release of preformed thyroid hormone, patients with cardiac disease and elderly patients are often treated with thionamides prior to RAI ablation. Occasionally, in patients with underlying cardiac disease, it can be necessary to reinstitute antithyroid drug therapy following radioactive iodine ablation. The standard practice is to withdraw the thionamide 4 to 6 days prior to RAI treatment and to reinstitute it 4 days after therapy is concluded. Administering antithyroid drug therapy following RAI treatment can result in a higher rate of posttreatment recurrence or persistent hyperthyroidism.[78]

Corticosteroid administration will blunt and delay the increase in antibodies to the TSH receptor, thyroglobulin, and thyroid peroxidase while reducing T_3 and T_4 concentrations following RAI. Bartalena and associates found no progression in ophthalmopathy in patients receiving prednisone after RAI compared with MMI (2% to 3% worsened), or no other treatment (5% with persistent worsening).[46] Theoretically, if shared thyroidal and orbital antigen is involved in the pathogenesis of Graves' ophthalmopathy, antigen released with RAI treatment could aggravate preexisting eye disease. Note also that thyroid ablation can decrease eye disease in the long term by removing the source of antigen, but it is unclear if RAI differs from surgery or thionamide for the risk of worsening eye disease.[79]

Destruction of the gland attenuates the hyperthyroid state, and hypothyroidism commonly occurs months to years following RAI.[80] The goal of therapy is to destroy overactive thyroid cells, and a single dose of 4,000 to 8,000 rads results in a euthyroid state in 60% of patients at 6 months or less. The remaining 40% become euthyroid within 1 year, requiring two or more doses. It is advisable that a second dose of RAI be given 6 months after the first RAI treatment if the patient remains hyperthyroid. Variables that influence the outcome of RAI include gender (men are less likely to develop hypothyroidism), race (blacks are more resistant to ^{131}I), the size of the thyroid, severity of disease, and perhaps the level of TSAb. The acute, short-term side effects of ^{131}I therapy are minimal and include mild thyroidal tenderness and dysphagia. Concern over the development of thyroid carcinoma and leukemia and increased risk of mutations and congenital defects now appears to be unfounded because long-term followup studies have not revealed increased risk for these complications.[81] Although RAI is very effective in the treatment of hyperthyroidism, long-term followup from Great Britain suggests that among patients with hyperthyroidism treated with RAI, mortality from all causes and mortality resulting from cardiovascular and cerebrovascular disease and fracture are increased.[82]

A common approach to Graves' hyperthyroidism is to administer a single dose of 5 to 15 mCi (80 to 200 microCi/g of tissue).[78] The optimal method for determining ^{131}I treatment doses for Graves' hyperthyroidism is unknown, and techniques have varied from a fixed dose to more elaborate calculations based on gland size, iodine uptake, and iodine turnover. In a trial of 88 patients with Graves' disease, no difference in outcome was seen among high or low, fixed or adjusted doses.[83] Thyroid glands estimated to weigh >80 g can require larger doses of RAI. Larger doses are likely to induce hypothyroidism and are seldom given outside the United States because of the imposition of stringent safety restrictions. For example, in the United Kingdom, a nursery school teacher is advised to stay out of school for 3 weeks following a 15-mCi dose of ^{131}I.[84]

EVALUATION OF THERAPEUTIC OUTCOMES: HYPERTHYROIDISM

After therapy (surgery, thionamides, or RAI) for hyperthyroidism has been initiated, patients should be evaluated on a monthly basis until they reach a euthyroid condition. Clinical signs of continuing thyrotoxicosis (tachycardia, weight loss, and heat intolerance, among others) or the development of hypothyroidism (bradycardia, weight gain, and lethargy, among others) should be noted. β-Blockers can be used to control symptoms of thyrotoxicosis until the definitive treatment has returned the patient to a euthyroid state. Once T_4 replacement is initiated, the goal is to maintain both the free T_4 level and the TSH concentration in the normal range. Once a stable dose of T_4 is identified, the patient can be followed up every 6 to 12 months.

Finally, a common, potentially confusing clinical situation should be mentioned. Why are the TSH concentrations suppressed in some patients who are clinically hypothyroid and who have a low free T_4 level? In patients with long-standing hyperthyroidism, the pituitary thyrotrophs responsible for making TSH become atrophic. The average amount of time required for these cells to resume normal functioning is 6 to 8 weeks.[85] Therefore if a thyrotoxic patient has his or her free T_4 concentration lowered rapidly, before the thyrotrophs resume normal function, a period of "transient central hypothyroidism" will be observed.

SPECIAL CONDITIONS

Graves' Disease and Pregnancy[86]

Inappropriate production of hCG is a cause of abnormal thyroid function tests during the first half of pregnancy, and hCG can cause either subclinical (normal T_4, suppressed TSH) or overt hyperthyroidism.[87,88] This is because of the homology of hCG and TSH, leading to hCG-mediated stimulation through the TSH receptor. Hyperthyroidism during pregnancy is almost solely caused by Graves' disease, with approximately 0.1% to 0.4% of pregnancies affected. Although the increased metabolic rate is usually well tolerated in pregnant women, two symptoms suggestive of hyperthyroidism during pregnancy are failure to gain weight despite good appetite, and persistent tachycardia. There is no increase in maternal mortality or morbidity in well-controlled patients; however, postpartum thyroid storm has been reported in about 20% of untreated individuals. Fetal loss is also more common, because spontaneous abortion and premature delivery are more common in untreated pregnant women, as are low-birth-weight infants and eclampsia. Transplacental passage of thyroid-stimulating antibodies can occur, causing fetal as well as neonatal hyperthyroidism.[89] An uncommon cause of hyperthyroidism is molar pregnancy; women present with a large-for-date uterus, and evacuation of the uterus is the preferred management approach.[90]

Because RAI is contraindicated in pregnancy and surgery is usually not recommended (especially during the first trimester), antithyroid drug therapy is usually the treatment of choice. MMI readily crosses the placenta and appears in breast milk.

PTU is considered to be the drug of choice in pregnancy, with the lowest possible doses used to maintain the maternal T_4 level in the high-normal range, but as described previously, there appears to be little difference between PTU and MMI.[89,91] To prevent fetal goiter and suppression of fetal thyroid function, PTU is usually prescribed in daily doses of 300 mg or less and tapered to 50 to 150 mg daily after 4 to 6 weeks. PTU doses of less than 200 mg daily are unlikely to produce fetal goiter.[91] Thioamide doses should be adjusted to maintain free T_4 within 10% of the upper normal limit of the nonpregnant reference range.[86] During the last trimester, TSAbs fall spontaneously, and some patients will go into remission so that antithyroid drug doses can be reduced. A rebound in maternal hyperthyroidism occurs in approximately 10% of women and can require more intensive treatment postpartum than in the last trimester of pregnancy.[89]

Neonatal and Pediatric Hyperthyroidism

Following delivery, some babies will be hyperthyroid because of placental transfer of TSAbs, which stimulates thyroid hormone production in utero and postpartum.[92,93] This is likely if the maternal TSAb titers were quite high. The disease is usually expressed 7 to 10

days postpartum, and treatment with antithyroid drugs (PTU 5 to 10 mg/kg per day or MMI 0.5 to 1 mg/kg per day) can be needed for as long as 8 to 12 weeks until the antibody is cleared (immunoglobulin G half-life is approximately 2 weeks). Iodide (potassium iodide 1 drop/day or Lugol solution 1 to 3 drops/day) and sodium ipodate can be used for the first few days to acutely inhibit hormone release.

Childhood hyperthyroidism is usually managed with either PTU or MMI. Long-term followup studies suggest that this form of therapy is quite acceptable, with 25% of a cohort experiencing remission every 2 years.[94]

Thyroid Storm

Thyroid storm is a life-threatening medical emergency characterized by decompensated thyrotoxicosis, high fever (often >39.4°C [103°F]), tachycardia, tachypnea, dehydration, delirium, coma, nausea, vomiting, and diarrhea.[19] Although Graves' disease and less commonly toxic nodular goiter are usually the underlying thyrotoxic pathology, at least two cases of subacute thyroiditis leading to thyroid storm have been reported.[95–97] Precipitating factors for thyroid storm include infection, trauma, surgery, RAI treatment, and withdrawal from antithyroid drugs. Although the duration of clinical decompensation lasts for an average duration of 72 hours, symptoms can persist up to 8 days. With aggressive treatment, the mortality rate has been lowered to 20%. The following therapeutic measures should be instituted promptly: (1) suppression of thyroid hormone formation and secretion, (2) antiadrenergic therapy, (3) administration of corticosteroids, and (4) treatment of associated complications or coexisting factors that precipitated the storm. Specific agents used in thyroid storm are outlined in Table 78–6. PTU in large doses is the preferred thionamide because it interferes with the production of thyroid hormones and blocks the peripheral conversion of T_4 to T_3. If patients are unable to take medications orally, the tablets can be crushed into suspension and instilled by gastric or rectal tube.[98] Iodides, which rapidly block the release of preformed thyroid hormone, should be administered after PTU is initiated to inhibit iodide use by the overactive gland. If iodide is administered first, it could theoretically provide substrate for even higher levels of hormone.

Antiadrenergic therapy with the short-acting agent esmolol is preferred, both because it can be used in the patient with pulmonary disease or at risk for cardiac failure and because its effects can be rapidly reversed.[99] Corticosteroids are generally recommended, although there is no convincing evidence of adrenocortical insufficiency in thyroid storm, and the benefits derived from steroids can be caused by their antipyretic action and their effect of stabilizing blood pressure.[19] General supportive measures, including acetaminophen as an antipyretic (do not use aspirin or other nonsteroidal antiinflammatory agents because they can displace bound-thyroid hormone), fluid and electrolyte replacement, sedatives, digitalis, antiarrhythmics, insulin, and antibiotics should be given as indicated. Plasmapheresis and peritoneal dialysis have been used to remove excess hormone (and to remove thyroid-stimulating immunoglobulins in Graves' disease) when the patient has not responded to more conservative measures, although these measures do not always work.[100]

TABLE 78-6 Drug Dosages Used in the Management of Thyroid Storm

Drug	Regimen
Propylthiouracil	900–1200 mg/day orally in four or six divided doses
Methimazole	90–120 mg/day orally in four or six divided doses
Sodium iodide	Up to 2 g/day IV in single or divided doses
Lugol solution	5–10 drops three times a day in water or juice
Saturated solution of potassium iodide	1–2 drops three times a day in water or juice
Propranolol	40–80 mg every 6 h
Dexamethasone	5–20 mg/day orally or IV in divided doses
Prednisone	25–100 mg/day orally in divided doses
Methylprednisolone	20–80 mg/day IV in divided doses
Hydrocortisone	100–400 mg/day IV in divided doses

HYPOTHYROIDISM

Hypothyroidism is defined as the clinical and biochemical syndrome resulting from decreased thyroid hormone production.[101] Overt hypothyroidism occurs in 1.5% to 2% of women and 0.2% of men, and its incidence increases with age. In the Third National Health and Nutrition Examination Survey, levels of serum TSH and total T_4 were measured in a representative sample of adolescents and adults (age 12 years or older). Among 16,533 people who neither were taking thyroid medication nor reported histories of thyroid disease, 3.9% had subclinical hypothyroidism (serum TSH >4.5 mIU/L; and T_4 normal), and 0.2% had "clinically significant" hypothyroidism (TSH >4.5 mIU/L; and T_4 <4.5 mcg/dL).[18] The vast majority of patients have primary hypothyroidism because of thyroid gland failure caused by chronic autoimmune thyroiditis. Special populations with higher risk of developing hypothyroidism include postpartum women, individuals with a family history of autoimmune thyroid disorders and patients with previous head and neck or thyroid irradiation or surgery, other autoimmune endocrine conditions (e.g., type 1 diabetes mellitus, adrenal insufficiency, and ovarian failure), some other nonendocrine autoimmune disorders (e.g., celiac disease, vitiligo, pernicious anemia, Sjögren's syndrome, and multiple sclerosis), primary pulmonary hypertension, and Down's and Turner's syndromes. Secondary hypothyroidism caused by pituitary failure is uncommon, but should be suspected in a patient with decreased levels of T_4 and inappropriately normal or low TSH levels. Most patients with secondary hypothyroidism because of inadequate TSH production will have clinical signs of more generalized pituitary insufficiency, such as abnormal menses and decreased libido, or evidence of a pituitary adenoma, such as visual field defects, galactorrhea, or acromegaloid features, but isolated TSH deficiency can be congenital or acquired as a result of autoimmune hypophysitis.[102] Generalized (peripheral and central) resistance to thyroid hormone is extremely rare.

Thyroid hormone is essential for normal growth and development during embryonic life. Uncorrected thyroid hormone deficiency during fetal and neonatal development results in mental retardation and/or cretinism. There is loss of physical and mental activity, as well as of cardiovascular, gastrointestinal, and neuromuscular function.

CLINICAL PRESENTATION OF HYPOTHYROIDISM

General

- Hypothyroidism can lead to a variety of end-organ effects with a wide range of disease severity, from entirely asymptomatic individuals to patients in coma with multisystem failure. In the adult, manifestations of hypothyroidism are varied and nonspecific. In the child, thyroid hormone deficiency can manifest as growth or intellectual retardation.

Symptoms

- Common symptoms of hypothyroidism include dry skin, cold intolerance, weight gain, constipation, and weakness. Complaints of lethargy, depression, fatigue or loss of ambition and energy are also common but are less specific. Muscle cramps, myalgia, and stiffness are frequent complaints of hypothyroid patients. Menorrhagia and infertility can present commonly in women.

Signs

- Objective weakness is common, with proximal muscles being affected more than distal muscles. Slow relaxation of deep tendon reflexes is common. The most common signs of decreased levels of thyroid hormone include coarse skin and hair, cold or dry skin, periorbital puffiness, and bradycardia. Speech is often slow as well as hoarse. Reversible neurologic syndromes such as carpal tunnel syndrome, polyneuropathy, and cerebellar dysfunction can also occur. Galactorrhea can be found in women.

Diagnosis

- In primary hypothyroidism, TSH serum concentration should be elevated. In secondary hypothyroidism, TSH levels can be within or below the reference range; when TSH bioactivity is altered, the levels reported by immunoassay can even be elevated.
- Free and/or total T_4 and T_3 serum concentrations should be low.

Other Tests

- Antithyroid peroxidase antibodies and antithyroglobulin antibodies are likely to be elevated in autoimmune thyroiditis.
- An increase in the TSH level is the first evidence of primary hypothyroidism. Many patients will have a free T_4 level within the normal range (compensated hypothyroidism) and few, if any, symptoms of hypothyroidism. As the disease progresses the free T_4 concentration will drop below the normal level. Interestingly, as a result of TSH stimulation, thyroidal production will shift toward greater amounts of T_3, and thus T_3 concentrations will often be maintained in the normal range in spite of a low T_4. The RAIU is not a useful test in the evaluation of a hypothyroid patient, as it can be low, normal, or even elevated.

CAUSES OF HYPOTHYROIDISM

Table 78–7 outlines the causes of hypothyroidism.

Chronic Autoimmune Thyroiditis

8 Autoimmune thyroiditis (Hashimoto's disease) is the most common cause of spontaneous hypothyroidism in the adult.[103] Patients can present with either goitrous thyroid gland enlargement and mild hypothyroidism, or thyroid gland atrophy and more severe thyroid hormone deficiency. Both forms of autoimmune thyroiditis probably result from cell- and antibody-mediated thyroid injury. The bulk of evidence suggests that the presence of specific defects in suppressor T-lymphocyte function leads to the survival of a randomly mutating clone of helper T lymphocytes, which are directed against normally occurring antigens on the thyroid membrane. Once these T lymphocytes interact with thyroid membrane antigen, B lymphocytes are stimulated to produce thyroid antibodies.[104]

TABLE 78-7 Causes of Hypothyroidism

Primary hypothyroidism
Hashimoto's disease
Iatrogenic hypothyroidism
Others
Iodine deficiency
Enzyme defects
Thyroid hypoplasia
Goitrogens
Secondary hypothyroidism
Pituitary disease
Hypothalamic disease

Antimicrosomal antibodies are present in virtually all patients with Hashimoto's thyroiditis and appear to be directed against the enzyme thyroid peroxidase.[105] These antibodies are capable of fixing complement and inducing cytotoxic changes in thyroid cells. Antibodies that are capable of stimulating thyroid growth through interaction with the TSH receptor can occasionally be found particularly in goitrous hypothyroidism; conversely, antibodies that inhibit the trophic effects of TSH are present in the atrophic type.

Iatrogenic Hypothyroidism

Iatrogenic hypothyroidism follows exposure to excessive amounts of radiation (radioiodine or external radiation) or surgery. Hypothyroidism occurs within 3 months to a year after ^{131}I therapy in most patients treated for Graves' disease. Thereafter it occurs at a rate of approximately 2.5% each year. External radiation therapy to the region of the thyroid using doses of greater than 2,500 cGy for therapy of neck carcinoma also causes hypothyroidism. This effect is dose-dependent, and more than 50% of patients who receive more than 4,000 cGy to the thyroid bed develop hypothyroidism. Total thyroidectomy causes hypothyroidism within 1 month.

Other Causes of Primary Hypothyroidism

Iodine deficiency, enzymatic defects within the thyroid gland, thyroid hypoplasia, and maternal ingestion of goitrogens during fetal development can cause cretinism. Early recognition and treatment of the resultant thyroid hormone deficiency is essential for optimal mental development.[106,107] Large-scale neonatal screening programs in North America, Europe, Japan, and Australia are now in place.[108] The frequency of congenital hypothyroidism in North America and Europe is 1 per 3,500 to 4,000 live births. In the United States, there are racial differences in the incidence of congenital hypothyroidism, with whites being affected seven times as frequently as blacks.

In the adult, hypothyroidism can rarely be caused by iodine deficiency and goitrogens. Rarely, iodine ingestion in the form of expectorants can lead to hypothyroidism. In sensitive persons (particularly those with autoimmune thyroiditis), the iodide blocks the synthesis of thyroid hormone, leading to an increased secretion of TSH and thyroid enlargement. Thus both iodine excess and iodine deficiency can cause decreased secretion of thyroid hormone.

Causes of Secondary Hypothyroidism

Pituitary Disease TSH is required for normal thyroid secretion. Thyroid atrophy and decreased thyroid secretion follow pituitary failure. Pituitary insufficiency can be caused by destruction of thyrotrophs by either functioning or nonfunctioning pituitary tumors, surgical therapy, external pituitary radiation, postpartum pituitary necrosis (Sheehan's syndrome), trauma, and infiltrative processes of the pituitary such as metastatic tumors, tuberculosis, histiocytosis, and autoimmune mechanisms.[109,110] In all these situations, TSH deficiency most often occurs in association with other pituitary hormone deficiencies. The identification of secondary hypothyroidism because of bexarotene use has led to recognition of the role of rexinoids and retinoids to cause dysregulation of TSH production.[22,111]

In most hypothyroid patients with pituitary disease, serum TSH concentrations are generally low or normal. A serum TSH concentration in the normal range is clearly inappropriate if the patient's T_4 is low.

Note that pituitary enlargement in hypothyroidism does not invariably indicate the presence of a primary pituitary tumor. Pituitary enlargement is seen in patients with severe primary hypothyroidism because of compensatory hyperplasia and hypertrophy of the thyrotrophs.[112] With thyroid hormone replacement therapy, serum TSH concentrations decline, indicating that the TSH secretion is not autonomous, and the pituitary resumes a more

normal configuration. These patients are easily separated from patients with primary pituitary failure by measuring a TSH level.

Hypothalamic Hypothyroidism TRH deficiency also causes a rare form of central hypothyroidism. In both adults and children it can occur as a result of cranial irradiation, trauma, infiltrative diseases, or neoplastic diseases.

TREATMENT

Hypothyroidism

■ PHARMACOLOGIC THERAPY

Desired Outcomes

The goals of therapy are to restore normal thyroid hormone concentrations in tissue, provide symptomatic relief, prevent neurologic deficits in newborns and children, and reverse the biochemical abnormalities of hypothyroidism.

General Approach

Any of the commercially available thyroid preparations accomplish this goal (Table 78–8); however, levothyroxine (L-thyroxine; T_4) is considered to be the drug of choice. The thyroid preparations are either natural (i.e., desiccated thyroid and thyroglobulin) or synthetic (levothyroxine, liothyronine, and liotrix) in origin. The availability of sensitive and specific assays for total and free hormone levels as well as TSH now allow more definitive dose titration to allow adequate replacement without inadvertent overdose. The response of TSH to TRH had been advocated for use by some for "fine-tuning" thyroid replacement, but this is not necessary if the sensitive immunoradiometric assays for TSH are used. Minimum clinical guidelines for the treatment of hypothyroidism have been published by the American Thyroid Association[56] and the American Association of Clinical Endocrinologists.[113]

Natural Thyroid Hormones

Desiccated thyroid is derived from hog, beef, or sheep thyroid gland. The *United States Pharmacopeia, 23rd Edition*, requires thyroid USP to contain 38 mcg (±15%) of levothyroxine and 9 mcg (±10%) of liothyronine for each 65 mg (1 grain) of the labeled content of thyroglobulin. Thyroglobulin USP should contain 36 mcg (±15%) of levothyroxine and 12 mcg (±10%) of liothyronine for each 65 mg (1 grain) of the labeled content of thyroglobulin. Not all generic brands can be bioequivalent, and switching among brands in patients stabilized on one product should be discouraged. Thyroid USP, as an animal protein–derived product, can be antigenic in allergic or sensitive patients. Even though desiccated thyroid is inexpensive, its limitations preclude it from being considered as a drug of choice for hypothyroid patients. Thyroglobulin is a purified hog-gland extract, but it has no clinical advantages and is not widely used.

Synthetic Thyroid Hormones

Levothyroxine (T_4; L-thyroxine) is the drug of choice for thyroid replacement and suppressive therapy because it is chemically stable, relatively inexpensive, and free of antigenicity, and has uniform potency. Whereas T_3 and not T_4 is the biologically more active form of thyroid hormone, levothyroxine administration results in a pool of thyroid hormone that is readily and consistently converted to T_3; in this regard levothyroxine can be thought of as a prohormone. The half-life of levothyroxine is approximately 7 days. This long half-life is responsible for a stable pool of prohormone and the need for only once-daily dosing with levothyroxine. Older studies with levothyroxine suggested that bioavailability was low and erratic; however, this product has been reformulated, and the average bioavailability is now approximately 80%.[114–116] The bioavailability of Synthroid, Levoxine, and generic levothyroxine preparations were compared in a blinded, randomized, four-way crossover trial.[117] The study was sponsored by the manufacturers of Synthroid, who have challenged the authors' conclusions that the levothyroxine preparations are bioequivalent and should be interchangeable for the majority of patients. However, because the relationship between T_4 concentration and TSH is not linear, very small changes in T_4 concentration can lead to substantial changes in TSH, which is a more accurate reflection of hormone replacement status. Currently, the Food and Drug Administration mandates that levothyroxine bioequivalency testing be done in normal volunteers (600 mcg in the fasted state) and three baseline free-T_4 concentrations be used to correct for endogenous T_4 production. Bioequivalency is based on the area under the curve (AUC) and

TABLE 78-8 Thyroid Preparations Used in the Treatment of Hypothyroidism

Drug/Dosage Form	Content	Relative Dose	Comments/Equivalency
Thyroid USP			
Armour Thyroid (T_4:T_3 ratio) 9.5 mcg:2.25 mcg, 19 mcg:4.5 mcg, 38 mcg:9 mcg, 57 mcg:13.5 mcg, 76 mcg:18 mcg, 114 mcg:27 mcg, 152 mcg:36 mcg, 190 mcg:45 mcg tablets	Desiccated beef or pork thyroid gland	1 grain (equivalent to 60 mcg of T_4)	Unpredictable hormonal stability, inexpensive generic brands may not be bioequivalent
Thyroglobulin			
Proloid 32-mg, 65-mg, 100-mg, 130-mg, 200-mg tablets	Partially purified pork thyroglobulin	1 grain	Standardized biologically to give T_4:T_3 ratio of 2.5:1; more expensive then thyroid extract; no clinical advantage
Levothyroxine			
Synthroid, Levothroid, and other generics 25-, 50-, 75-, 88-, 100-, 112-, 125-, 137-, 150-, 175-, 200-, 300-mcg tablets; 200- and 500-mcg/vial injection	Synthetic T_4	50–60 mcg	Stable; predictable potency; generics are bioequivalent; when switching from natural thyroid to L-thyroxine, lower dose by $^1/_2$ grain; variable absorption between products; half-life = 7 days, so daily dosing; considered to be drug of choice
Levoxyl, Thyro-Tabs, Unithroid			
Liothyronine			
Cytomel 5-, 25-, and 50-mcg tablets	Synthetic T_3	15–37.5 mcg	Uniform absorption, rapid onset; half-life = 1.5 days, monitor TSH assays
Liotrix			
Thyrolar $^1/_4$-, $^1/_2$-, 1-, 2-, and 3-strength tablets	Synthetic T_4:T_3 in 4:1 ratio	50–60 mcg T_4 and 12.5–15 mcg T_3	Stable; predictable; expensive; lacks therapeutic rationale because T_4 is converted to T_3 peripherally

TSH, thyroid-stimulating hormone; T_3, triiodothyrine; T_4, thyroxine.

maximum concentration (C_{max}) of T_4 out to 48 hours. Approximately 70% of the AUC is derived from endogenous production. TSH is not considered, and it is now very clear that T_4 is too insensitive as a measure of bioequivalency.[118,119] To avoid over- and undertreatment, once a product is selected, therapeutic interchange should be discouraged. Currently, there are nine levothyroxine products available, and a number of permutations for interchange are available considering that there are AB1, AB2, AB3 and BX products available as no reference listed drug is mandated in bioequivalency testing. The time to maximal absorption is 2 hours, and this should be considered when T_4 and TSH concentrations are determined. Mucosal diseases such as sprue, diabetic diarrhea, and ileal bypass surgery can also reduce absorption. Cholestyramine, calcium carbonate, sucralfate, aluminum hydroxide,[120] ferrous sulfate,[121] soybean formula,[122] and dietary fiber supplements[123] can also impair the absorption of levothyroxine from the gastrointestinal tract. Acid suppression with histamine blockers and proton pump inhibitors can also reduced levothyroxine absorption. Drugs that increase T_4 clearance include rifampin, carbamazepine, and possibly phenytoin. Selenium deficiency and amiodarone can block the conversion of T_4 to T_3.

Liothyronine (T_3) is chemically pure with known potency and has a shorter half-life of 1.5 days. Although it is widely used diagnostically in the T_3-suppression test, T_3 has some clinical disadvantages, including a higher incidence of cardiac adverse effects, higher cost, and difficulty in monitoring with conventional laboratory tests. Liotrix is a combination of synthetic T_4 and T_3 in a 4:1 ratio that attempts to mimic natural hormonal secretion. It is chemically stable and pure and has a predictable potency. The major limitations to this product are high cost and lack of therapeutic rationale because approximately 35% of T_4 is peripherally converted T_3.

Trials comparing levothyroxine alone to a combination of levothyroxine plus partial replacement with liothyronine (T_3) have generally shown that combinations of T_4 plus T_3 are no better than T_4 alone.[124,125] Clyde and colleagues in a trial of combination therapy, when compared with levothyroxine alone, treatment of primary hypothyroidism with combination levothyroxine plus liothyronine demonstrated no beneficial changes in body weight, serum lipid levels, hypothyroid symptoms as measured by a health-related quality of life questionnaire, and standard measures of cognitive performance.[125]

Dosing and Monitoring During the mid-1980s the average dose of levothyroxine was approximately 160 mcg/day. With the advent of more sensitive assay methods for TSH and the reformulation of levothyroxine, it is now apparent that many patients have been treated with excessive amounts of levothyroxine. More recent studies suggest that the average maintenance dose for most adults should be closer to about 125 mcg per day.[101] Indeed, as many as one-third of patients receiving levothyroxine 150 mcg daily will be over-replaced. There is, however, a wide range of replacement doses, necessitating individualized therapy and appropriate TSH monitoring to determine an adequate but not excessive dose.

The initial dose of levothyroxine is dependent on the patient's age, and the presence of associated disorders, as well as the severity and duration of hypothyroidism.[126] Most patients will require approximately 1.7 mcg/kg/day once they reach steady state for full replacement. In young patients with long-standing disease and patients older than 45 years of age without known cardiac disease, therapy should be initiated with 50 mcg daily of levothyroxine and increased to 100 mcg daily after 1 month. The recommended initial daily dose for older patients or those with known cardiac disease is 25 mcg per day titrated upward in increments of 25 mcg at monthly intervals to prevent stress on the cardiovascular system. Some patients can experience an exacerbation of angina with higher doses of thyroid hormone. Although the TSH is very sensitive for under- or overreplacement, clinicians often fail to alter the dose of T_4 based on TSH clearly outside of the normal range.[127,128]

Patients with subclinical or mild hypothyroidism (seen more commonly in the elderly and women) have no or few signs or symptoms, normal serum T_3 and T_4 concentrations, and an elevated basal TSH concentration.[129,130] The prevalence of this disorder in the NHANES III study was found to be 4.3%.[18] Although the treatment of subclinical hypothyroidism is controversial, patients presenting with marked elevations in TSH (>10 mIU/L) and high titers of thyroperoxidase antibody (TPO Ab) or prior treatment with ^{131}I can be most likely to benefit from treatment. Other patients who can improve with replacement include those with mild symptoms of hypothyroidism and depression. It should be noted that some studies find that only one of four treated patients experienced improvement.[131] Conservative treatment goals in this situation would be to maintain serum T_4 and T_3 levels in the normal range and reduce TSH to a value of 1 mIU/L.

Once euthyroidism is attained, the daily maintenance dose of levothyroxine does not fluctuate greatly. As patients age, the dosing requirement can need to be reduced.[113] The ability to measure serum TSH concentrations has improved the accuracy with which thyroid hormone replacement can be monitored. Many clinicians now consider serum TSH concentration to be the most sensitive and specific monitoring parameter for adjustment of levothyroxine dose. Plasma TSH concentrations begin to fall within hours and are usually normalized within 2 weeks but can take up to 6 weeks in some patients, depending on the baseline value. TSH and T_4 concentrations are both used to monitor therapy, and they should be checked every 6 weeks until a euthyroid state is achieved. Serum T_4 concentrations can be useful in detecting noncompliance, malabsorption, or changes in levothyroxine product bioequivalence. An elevated TSH concentration indicates insufficient replacement. The appropriate dose maintains the TSH concentration in the normal range. T_4 disposal is accelerated by nephritic syndrome, other severe systemic illnesses, and several antiseizure medications (phenobarbital, phenytoin, and carbamazepine) and rifampin. Pregnancy increases the T_4 dose requirement in 75% of women, probably because of increased degradation by the placental deiodinase. Initiating postmenopausal hormone replacement therapy increases the dose needed in 35% of women, perhaps because of an increased circulating T_4-binding globulin level. Patient noncompliance with prescribed T_4, the most common cause of inadequate treatment, might be suspected in patients with a dose that is higher than expected, variable thyroid function test results that do not correlate well with prescribed doses, and an elevated serum thyrotropin concentration with serum-free T_4 at the upper end of the normal range, which can suggest improved compliance immediately before testing because of a lag in the thyrotropin response. The metabolism of other pharmacologic agents can be altered in patients with hypothyroidism. The mechanism might be decreased expression of hepatic enzymes involved in drug metabolism, as seen in hypothyroid rats. As a result, increased sensitivity to anesthetic and sedative agents and higher serum levels of phenytoin have been reported. Hypothyroidism can also cause higher serum digoxin values, an effect attributed to a decreased volume of drug distribution. Conversely, hypothyroidism might decrease sensitivity to warfarin because of slowed metabolism of the vitamin K–dependent clotting factors, and restoration of euthyroidism can then increase the warfarin dose requirement.

In patients with hypothyroidism caused by hypothalamic or pituitary failure, alleviation of the clinical syndrome and restoration of serum T_4 to the normal range are the only criteria available for estimating the appropriate replacement dose of levothyroxine. Concurrent use of dopamine, dopaminergic agents (bromocriptine), somatostatin or somatostatin analogs (octreotide), and corticosteroids suppresses TSH concentrations and can confound the interpretation of this monitoring parameter.[113]

TSH-suppressive levothyroxine therapy can also be given to patients with nodular thyroid disease and diffuse goiter, to patients with a

history of thyroid irradiation, and to patients with thyroid cancer. The rationale for suppression therapy is to reduce TSH secretion, which promotes growth and function in abnormal thyroid tissue. In patients with solitary nodules who have not received radiation, TSH should be suppressed to 0.05 to 0.1 mIU/L in premenopausal women and in men <60 years old. A dose of levothyroxine of 100 to 150 mcg per day is usually sufficient. In men older than 60 years of age and postmenopausal women, TSH levels should be reduced to 0.1 to 0.3 mIU/L because of the risk of more serious adverse effects in this population and reduced clearance of levothyroxine with advanced age. Levothyroxine can be given in nontoxic MNG to suppress the TSH to low-normal levels of 0.5 to 1 mIU/L if the baseline TSH is >1 mIU/L. Goiter size and thyroid volume can be reduced with suppression therapy. Diffuse goiter associated with autoimmune thyroiditis can also be treated with levothyroxine to reduce goiter size and thyroid volume. In patients with follicular or papillary thyroid cancer, current recommendations are to suppress the TSH to <0.02 mIU/L. Doses of levothyroxine of up to 2.2 to 2.5 mcg/kg can be needed to provide TSH levels of <0.02 mIU/L in this population, and free T_3 and T_4 levels are useful in detecting hyperthyroidism.[132]

Adverse Effects Serious untoward effects are unusual if dosing is appropriate and the patient is carefully monitored during initial treatment. Levothyroxine replacement in athyrotic hypothyroid patients restores systolic and diastolic left ventricular performance within 2 weeks, and the use of levothyroxine can increase the frequency of atrial premature beats but not necessarily ventricular premature beats. Excessive doses of thyroid hormone can lead to heart failure, angina pectoris, and myocardial infarction; rarely, the latter can be caused by coronary artery spasm. Allergic or idiosyncratic reactions can occur with the natural animal-derived products such as desiccated thyroid and thyroglobulin, but these are extremely rare with the synthetic products used today. The 0.05-mg Synthroid tablet is the least allergenic (caused by a lack of dye and few excipients) and should be tried in the patient suspected to be allergic to thyroid hormone.

Hyper-remodeling of cortical and trabecular bone caused by hyperthyroidism leads to reduced bone density and can increase the risk of fracture. Compared with normal controls, excess exogenous thyroid hormone results in histomorphometric and biochemical changes similar to those observed in osteoporosis and untreated hyperthyroidism; however, at routinely used replacement doses, bone mineral density loss is less than that seen with untreated hyperthyroidism and only slightly greater than in controls.[133,134] The risk for this complication of therapy seems to be related to the dose of levothyroxine, patient age, and gender. Markers for bone turnover include urinary cross-linked *N*-telopeptides, pyridinoline of type I collagen, osteocalcin, and bone-specific alkaline phosphatase. When doses of levothyroxine are used to suppress TSH concentrations to below-normal values (less than 0.3 mIU/L) in postmenopausal women, this adverse effect is more likely to be seen. Cortical bone is affected to a greater degree than trabecular bone at suppressive doses of 1-thyroxine. In contrast, it appears to be much less likely in men and in premenopausal women. Maintaining the TSH between 0.7 and 1.5 mIU/L with approximately 150 mcg/day of levothyroxine does not alter bone mineral density in premenopausal women.

SPECIAL CONDITIONS

Myxedema Coma

Myxedema coma is a rare consequence of decompensated hypothyroidism.[135,136] Clinical features include hypothermia, advanced stages of hypothyroid symptoms, and altered sensorium ranging from delirium to coma. Mortality rates of 60% to 70% necessitate immediate and aggressive therapy. Traditionally, the initial treatment has been intravenous bolus levothyroxine 300 to 500 mcg. However, as deiodinase activity is markedly reduced, impairing T_4 to T_3 conversion, initial treatment with intravenous T_3 or a combination of both hormones has also been advocated.[136] Glucocorticoid therapy with intravenous hydrocortisone 100 mg every 8 hours should be given until coexisting adrenal suppression is ruled out. Consciousness, lowered TSH concentrations, and normal vital signs are expected within 24 hours. Maintenance doses of levothyroxine are typically 75 to 100 mcg given intravenously until the patient stabilizes and oral therapy is begun. Supportive therapy must be instituted to maintain adequate ventilation, euglycemia, blood pressure, and body temperature. Any underlying disorder, such as sepsis or myocardial infarction, obviously must be diagnosed and treated.

Congenital Hypothyroidism[137]

In congenital hypothyroidism, full maintenance therapy should be instituted early to improve the prognosis for mental and physical development.[138] The average maintenance dose in infants and children depends on the age and weight of the child. Several studies demonstrate that aggressive therapy with levothyroxine is important for normal development and current recommendations are for initiation of therapy within 45 days of birth at a dose of 10 to 15 mcg/kg per day.[108] This dose is used to keep T_4 concentrations at about 10 mcg/dL within 30 days of starting therapy and is associated with improved intelligence quotients (IQs) in treated infants. The dose is progressively decreased to a typical adult dose as the child ages, the adult dose being given in the age range of 11 to 20 years.

Hypothyroidism in Pregnancy[86]

Hypothyroidism during pregnancy leads to an increased rate of stillbirths and possibly lower psychologic scores in infants born of women who received inadequate replacement during pregnancy.[139] Thyroid hormone is necessary for fetal growth and must come from the maternal side during the first 2 months of gestation. Although liothyronine can cross the placental membrane slightly better than levothyroxine, the latter is considered to be the drug of choice. The objective of treatment is to decrease TSH to 1 unit/mL and maintain free T_4 concentrations in the normal range. Based on elevated TSH levels during pregnancy, it was found that the mean dose of levothyroxine had to be increased by 36 mcg/day to suppress TSH into the normal range. Increased production of binding proteins, a marginal decrease in free hormone concentration, modification of peripheral thyroid hormone metabolism, and increased T_4 metabolism by the fetal-placental unit also contributes to increased thyroid hormone demand and the need for increased doses decreases after delivery.[87] Up to 60% of women need to have levothyroxine dose adjustment during pregnancy. Upward adjustment will be needed by week 8 of pregnancy. After delivery the levothyroxine can need to be reduced based on T_3 concentrations and measurement of TSH, typically approximately 6 to 8 weeks after delivery.[86]

Effects of Hypothyroidism on Selected Medications

Hypothyroidism can affect the metabolism and clinical efficacy of several medications. Digitalis preparations have a decreased volume of distribution in the hypothyroid state, resulting in increased sensitivity to the digitalis effect. Therefore, many hypothyroid patients achieve a therapeutic effect at lower digitalis doses. Insulin degradation can be delayed in hypothyroidism, thereby requiring a lower insulin dose. Hypothyroidism delays the catabolism of clotting factors, and if a patient stabilized on warfarin is made euthyroid with levothyroxine, the patient can become excessively anticoagulated. Respiratory depressants such as barbiturates, phenothiazines, and opioid analgesics should be avoided, because increased sensitivity can increase carbon dioxide retention and precipitate myxedema coma.

RECOMBINANT TSH IN THYROID CANCER

Patients with previously treated differentiated (papillary, follicular, or their respective variants) thyroid carcinoma require lifelong monitoring for recurrent disease.[140,141] Two diagnostic tests that play a central role in followup of these patients—serum thyroglobulin measurement and radioiodine whole body scanning—are most accurate during TSH stimulation. Temporary discontinuation of thyroid hormone therapy was previously the sole effective approach for TSH-stimulated testing. However, hormone withdrawal is associated with the morbidity of hypothyroidism and occasional tumor progression. The introduction of recombinant TSH (rTSH)-stimulated testing offers an alternative therapy. Recent clinical trials have shown that the sensitivity of combined rTSH-stimulated radioiodine scanning and serum thyroglobulin measurement has nearly equivalent sensitivity to testing after thyroid hormone withdrawal.[111,142] Furthermore, measurement of the rTSH-stimulated thyroglobulin concentration is a more sensitive way to detect residual thyroid cancer or normal tissue than thyroglobulin measurement or thyroid hormone therapy alone. Post-thyroidectomy adjuvant radioiodine therapy can also be administered following rTSH, instead of thyroid hormone withdrawal, with equivalent rates of remnant ablation.[143] Patients in whom thyroid hormone withdrawal would be contraindicated can also be successfully treated with radioiodine following rTSH.[144]

NONTHYROIDAL ILLNESS

A wide variety of abnormalities of hypothalamic-pituitary-thyroid function, serum thyroid hormone binding, and extrathyroidal thyroid hormone metabolism occur in patients with nonthyroidal illness.[11,12] These abnormalities frequently result in decreased serum T_3 concentrations and, with more severe nonthyroidal disease, lead to a decreased serum free T_4 concentration as well. Serum TSH concentrations are usually within the normal range, although low levels can occur with severe or critical illness. The presence of coexisting primary hypothyroidism can be recognized in patients who have other illnesses by an elevation in the TSH concentration.

The degree and extent of the abnormality in thyroid function generally correlates with the severity of the nonthyroidal illness. These conditions are frequently referred to as the "euthyroid sick syndrome." However, it is likely that these changes represent adaptive forms of hypothyroidism that serve to reduce the availability of thyroid hormones to lessen the catabolic impact of the nonthyroidal illness.

Decreased serum T_3 concentrations occur in patients with both acute and chronic illnesses. The fundamental cause of decreased serum T_3 concentrations in these situations is decreased extrathyroidal conversion of T_4 to T_3, normally mediated by T_4–5'-deiodinase. A circulating inhibitor of this enzyme, perhaps interleukin-6, is present in patients with nonthyroidal illness.[145] Serum total and free T_4 concentrations are usually normal in mild illness. The serum reverse T_3 concentration is characteristically high because the same enzyme, 5'-deiodinase, that is necessary to convert T_4 to T_3, is necessary to convert reverse T_3 to its breakdown products.

Low serum T_4 is seen in most critically ill patients.[146–148] This change is caused by diminished serum T_4 synthesis as well as impaired binding to serum transport proteins, resulting either from decreased serum concentrations of thyroid-binding globulin, thyroid-binding prealbumin, or albumin, or from inhibitors of T_4 binding. The free T_4 concentration is generally normal early in critical illness but also declines with more severe disease. This more severe degree of hypothyroidism, which occurs in severely ill patients, produces a greater reduction in thyroid hormone availability. The low serum T_4 concentrations in patients with nonthyroidal illness indicates a grave prognosis. In two studies, more than 60% of hospitalized patients with a low serum free T_4 index died. Although controversial, T_4 or T_3 supplementation has been of no benefit in this situation and in fact has increased morbidity.

To confuse matters, some patients with nonthyroidal illness have elevation of their serum T_4 concentration. Most commonly, this is seen in patients with psychiatric disorders during acute psychotic breaks. Thyroid hormone levels return to normal within 2 weeks after successful treatment of the underlying psychiatric disease. The occurrence of these abnormalities requires that care be taken in diagnosing hypothyroidism or hyperthyroidism in patients who have nonthyroidal illnesses.

GOITROUS THYROID DISEASE

Endemic goiter is the major thyroid disease throughout the world, affecting more than 200 million people. Many goitrous glands contain one or more nodules. The introduction of iodide supplementation has eliminated goiter as a major medical problem in developed countries, although it continues to be a problem in developing countries with geographic positions that make them more susceptible to iodide deficiency. In 1924, Marine postulated that periods of iodide deficiency resulted in cyclic hyperplasia and involution of thyroid follicular cells with eventual development of nodular hyperplasia.[44,149] This hypothesis is still used to explain goiter formation today. Whatever the specific cause, the final common pathway appears to result from an inadequate thyroid hormone secretion with compensatory TSH secretion and eventual thyroid gland enlargement. The essential factor for the conversion of a hyperplastic iodine-deficiency goiter into a colloid goiter appears to be an acute reduction of TSH stimulation; therefore, any situation that would result in a cyclical increase and decrease in TSH secretion might eventually result in the production of a nodular goiter.

There has been an interest in the possibility that growth factors other than TSH play a role in the development of a goiter. Immunoglobulin fractions capable of stimulating thyroid growth have been found in patients with nontoxic goiter and Graves' disease. In these patients, thyroid growth–promoting immunoglobulin titers correlate with goiter size rather than with the thyroid hormone concentration.

Sporadic goiter is defined as a goiter occurring in a nonendemic goiter region. Although a number of known goitrogens and errors in thyroid hormone biosynthesis can cause goiter, the majority of cases of sporadic goiter have no known etiology.

Treatment of all goiters is a trial of thyroid hormone suppression in an effort to eliminate TSH as a possible stimulus for continued thyroid growth. Large, long-standing goiters seldom undergo significant reduction in size. If the patient is symptomatic (with dysphagia or dyspnea) or there is a question of malignant thyroid involvement, surgery is recommended.

PHARMACOECONOMIC CONSIDERATIONS

Although the initial expense of surgery would seem to make it the most expensive treatment option, the relapse rates for thionamides and RAI are higher and in longer-term followup, there is not much difference between treatment options nor patients' opinions concerning treatment preferences.[150] The cost proportion between the medical and surgical treatment in younger patients is 1:2.5 (1 = US $1126) before and 1:1.3 (1 = US $2284) after inclusion of the relapse costs. The proportion between the medical, surgical, and ^{131}I treatment in older patients is 1:2.5:1.6 (1 = US $1164) before and 1:1.6:1.4 (1 = US $1972) after inclusion of the relapse costs.

CLINICAL CONTROVERSIES

Although the current FDA standards of bioavailability for T_4 products suggest that several products are bioequivalent, the relationship between T_4 serum concentration and TSH response suggests that the products are not truly bioequivalent. New standards of bioequivalency might need to be developed for drug products such as T_4.

Combination therapy of T_4 plus T_3 for hypothyroidism seems to improve cognitive function over monotherapy with T_4; however, there are not corresponding improvements in biochemical markers of thyroid hormone nor differences in TSH response.

Multiple studies have addressed the role of thyroid supplementation in critically ill patients with cardiac disease, sepsis, pulmonary disease (e.g., acute respiratory distress syndrome), or severe infection, or with burn and trauma patients. In spite of a very large number of published studies, it is very difficult to form clear recommendations for treatment with thyroid hormone in the intensive care unit.

EVALUATION OF THERAPEUTIC OUTCOMES

Patients on optimal thyroid hormone replacement therapy should have TSH and free T_4 serum concentrations in the normal range with idiopathic hypothyroidism and Hashimoto's thyroiditis. Those who are being treated for thyroid cancer should have TSH suppressed to very low levels and thyroglobulin should be undetectable. Given the half-life of 7 days of T_4, the appropriate monitoring interval is no more often than 4 weeks. The signs and symptoms of hypothyroidism should be improved or absent (see clinical presentation of hypothyroidism, above), although this can take several months for most to improve.

ABBREVIATIONS

ClO_4^-: perchlorate

DIT: diiodotyrosine

FSH: follicle-stimulating hormone

$G_s\alpha$: α subunit of the stimulatory guanine-nucleotide-binding protein

hCG: human chorionic gonadotropin

HLA: human leukocyte antigen

^{131}I: sodium iodide 131

L-Thyroxine: levothyroxine

LH: luteinizing hormone

MIT: monoiodotyrosine

MMI: methimazole

MNG: multinodular goiter

PRTH: pituitary resistance to thyroid hormone

PTU: propylthiouracil

RAI: radioactive iodine

RAIU: radioactive iodine uptake

rTSH: recombinant thyroid-stimulating hormone

SCN^-: thiocyanate

SSKI: saturated solution of potassium iodide

T_3: triiodothyronine

T_4: thyroxine

TBG: thyroid-binding globulin

TG: thyroglobulin

TPO Ab: thyroperoxidase antibody

$TR\beta_2$, $TR\beta_1$, $TR\alpha_1$: thyroid hormone receptors

TRH: thyrotropin-releasing hormone

TSAb: thyroid-stimulating antibody

TSH: thyroid-stimulating hormone

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